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Review article

Maternal effects in mammals: Broadening our understanding of offspring programming

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ABSTRACT

The perinatal period is a sensitive time in mammalian development that can have long-lasting consequences on offspring phenotype via maternal effects. Maternal effects have been most intensively studied with respect to two major conditions: maternal diet and maternal stress. In this review, we shift the focus by discussing five major additional maternal cues and their influence on offspring phenotype: maternal androgen levels, photoperiod (melatonin), microbiome, immune regulation, and milk composition. We present the key findings for each of these topics in mammals, their mechanisms of action, and how they interact with each other and with the maternal influences of diet and stress. We explore their impacts in the contexts of both predictive adaptive responses and the developmental origins of disease, identify knowledge gaps and research opportunities in the field, and place a particular emphasis on the application and consideration of these effects in non-model species and natural ecological systems.

1. Introduction

To maximize fitness, animals must balance individual condition, reproduction, and survival against environmental challenges, energetic demands, and competition. Variable phenotypes that may provide fitness advantages are continually sculpted by environmental forces. Over evolutionary time, natural selection determines the prevalence of genotypes present in the population. However, phenotypic plasticity allows for individual adaptation to environmental pressures on a shorter timescale – within an animal's lifetime. A major route of such individual adaptation is through maternal effects whereby the maternal experience – rather than genetic heredity alone – shapes offspring phenotype (Mousseau and Fox, 1998). If the maternal environment is predictive of the conditions offspring will experience, maternal cues in early life (gestational and/or early postnatal) can influence offspring development to best suit future conditions, termed "predictive adaptive responses" (Gluckman et al., 2005).

Maternal programming is heavily researched in two general areas in mammals: perinatal diet and stress. In a Web of Science search (April 2021) with "maternal programming" as a topic (title, abstract, or keywords), 38% of these publications had "stress" and 41% had "diet" as topics. Studies on programming by maternal diet have largely focused on experimental manipulations of dietary macronutrients (fat, sugars) in laboratory rodent models to create conditions of undernutrition or overnutrition. These experiments particularly emphasize high fat diet consumption as a model for Western human diets, and have been the focus of substantial examination and review (Chang et al. 2008, Sullivan et al. 2015, Barrett et al. 2016). Studies on programming by maternal stress have focused on maternal adversity and circulating levels of glucocorticoids (GCs; cortisol or corticosterone). GCs cross the placenta to the fetus and profoundly influence offspring development and phenotype. Maternal stress axis function can also produce variation in maternal care behavior and therefore influence postnatal offspring development (Ladd et al., 2000; Liu et al., 1997; Xiong and Zhang,

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2013). The associations between maternal stress and offspring phenotype have been examined in many systems, both in the laboratory and in natural contexts, and have been thoroughly reviewed elsewhere (Harris and Seckl, 2011; Love et al., 2013; Moisiadis and Matthews, 2014; Sullivan et al., 2015).

In this review, we highlight the diversity and complexity of maternal effects by examining five additional routes of maternal programming with the potential for considerable explanatory power in mammals: 1) prenatal androgen exposure, 2) maternal photoperiod (melatonin), 3) the maternal microbiome, 4) the maternal immune system, and 5) maternal milk. As maternal systems do not work in isolation – and may in fact have overlapping, synergistic, or antagonistic effects on offspring phenotype – we consider the ways in which these five routes interact with one another as well as with the major influences of maternal diet and stress. We review their known impacts on offspring phenotype in humans and laboratory rodent models, as well as their effects in mammals outside of traditional laboratory models (Table 1). Finally, we aim to identify knowledge gaps and research opportunities in the field, placing a particular emphasis on their application in natural ecological systems. This approach allows for an examination of the biological generality of maternal programming effects and insights into the mechanisms of phenotypic plasticity across mammals.

2. Maternal androgens

Androgens are a class of steroid hormones, the primary of which is testosterone in mammals. They exert biological effects by binding to androgen receptors and/or by aromatization to estradiol and binding to estrogen receptors (Naftolin et al., 1975). During gestation, fetal androgen exposure stems from circulating maternal androgens as well as testicular production of androgens in male offspring. Circulating maternal androgens cross the placenta, interact with fetal tissues, and maternal levels can vary independent of fetal sex (Glass and Klein, 1981). As such, there can be individual variation in prenatal androgen exposure for both males and females. The amount of maternal androgens that cross the placenta varies by species according to placental ability to aromatize and inactivate androgens (Abbott et al., 2008; Despres et al., 1984; France et al., 1987; Yalcinkaya et al., 1993). Levels of maternal androgens that exceed the functional capacity of placental inactivation are thus transmitted to the fetus and able to exert programming effects on fetal development and offspring phenotype (Abbott et al., 2008; Hakim et al., 2017).

While prenatal androgen exposure has classically been associated with changes in external morphology, including the index to ring finger (2D:4D) ratio (Swift-Gallant et al., 2020), longer anogenital distances (Dean and Sharpe, 2013; van den Driesche et al., 2011), and at high levels in particular programming windows, genital masculinization in females (Abbott et al., 2005; Zambrano et al., 2014), it is also associated with changes in the brain and behavior. As early as 1959, Phoenix et al. demonstrated that exposure to androgens during gestation led to permanent sexually differentiated mating behavior in guinea pigs (*Cavia porcellus*), termed the "organizational effects" of androgens on behavior. This conceptual framework has generally held up until present, though the scope has expanded considerably (Arnold, 2009). Prenatal androgens can influence both the structural development of the brain and regulation of the hypothalamic-pituitary-gonadal axis (HPG axis; reproductive axis). Brain structural changes are enacted by androgenic regulation of the growth of axons and dendrites, number of synapses, and neuronal cell death during development (Arnold, 2009; Forger, 2006; Simerly, 2002). The precise cellular mechanisms by which these processes are influenced by sex hormones is an extensive area of research, and detailed reviews can be found elsewhere (Forger, 2006; McCarthy et al., 2009; VanRyzin et al., 2018). Generally, the effects of androgens on the developing brain include both masculinization effects, where male-typical development occurs, and defeminization effects, where female-typical development is suppressed. For example, in female rats, brain regions that are typically sexually dimorphic (e.g. anteroventral periventricular nucleus, medial preoptic area of the hypothalamus) can be induced to develop into the male-typical morphology with prenatal androgen treatment (Simerly, 2002).

2.1. Factors shaping maternal androgens and impacts on offspring phenotype

A great deal of our understanding of the effects of prenatal androgens has come from experimental manipulation of androgen levels in pregnant female laboratory animals treated with either dihydrotestosterone (a non-aromatizable androgen) or testosterone propionate (Abbott et al., 2005; Zambrano et al., 2014). However, natural variation in maternal androgen levels does occur as well. One of the drivers of maternal variation in androgen levels is the social environment. Glucocorticoid levels have received much attention as a biomarker of social status, competition, or social stability, but maternal androgens also offer valuable insights into dynamics of the social environment. In female spotted hyenas (*Crocuta crocuta*), socially dominant individuals have higher androgen levels during late gestation than subordinate females, but no status-related differences in GCs. These gestational maternal androgens levels are positively associated with offspring aggression (Dloniak et al., 2006). In guinea pigs, an unstable social environment during pregnancy – i.e. an environment where other female cage mates are alternated regularly as opposed to a consistent social group – results in lower levels of maternal dehydroepiandrosterone (DHEA; a testosterone precursor and weak androgen) but does not affect maternal cortisol levels (Kaiser et al., 2003). Male offspring born to the unstable-housed females show delayed behavioral development and higher circulating cortisol levels in early life (Kaiser and Sachser, 2001), whereas female offspring have more masculine behavior and higher testosterone, but no differences in cortisol levels (Kaiser and Sachser, 1998).

Additionally, there is evidence that maternal glucocorticoid and androgen levels can co-vary together. This is perhaps surprising, because androgens have often been linked with stress-axis suppression, and similarly, the stress-axis has often been linked with reproductive suppression (Handa et al. 1994; Lund et al. 2004). However, further work has shown that the negative relationship between androgens and the stress-axis is species-specific. A study in pregnant women found that cortisol and testosterone are positively correlated in the amniotic fluid regardless of the child's sex (Bergman et al. 2010). There was a significant positive effect of prenatal testosterone levels on fear reactivity in the male children, but no effect in female children, and no effect of cortisol levels (Bergman et al. 2010). In Antarctic fur seals (*Arctocephalus gazella*), pregnant females living in high density social environments have higher levels of both cortisol and testosterone than those living in low densities (Meise et al. 2016). The high density mothers also had offspring with higher testosterone levels, but not cortisol, leading the authors to suggest that testosterone may be the more salient cue influencing offspring phenotype (Meise et al. 2016). These studies raise the possibility that, in some prior work on maternal programming where maternal cortisol was the only hormone quantified, maternal cortisol levels may not actually be the causal mechanism in offspring programming as they can covary with androgen levels.

Maternal age has alsobeen associated with differences in androgen levels during pregnancy. Androgen levels in pregnant women decrease with increasing maternal age, regardless of parity (Carlsen et al., 2003). A similar inverse relationship between maternal age and androgen levels during pregnancy is reported in marmosets (*Callithrix geoffroyi*). In these marmosets, increased maternal androgens are also associated with offspring behavioral effects – a decline in rough-play behavior in offspring (Birnie et al., 2012). In contrast, prenatal testosterone treatment is associated with an increase in rough-play behavior in rhesus macaque (*Macaca mulatta*) offspring (Birnie et al., 2012; Goy et al., 1988) demonstrating the species-specific nature of androgenic impacts

Table 1
Maternal cues, programming routes, and their effects on offspring phenotype in mammals.

				Growth; metabolism; endocrine function	Timing of sexual maturation	Reproductive axis function; postnatal androgen levels	Stress axis function; postnatal glucocorticoid levels	Behavior	Neurodevelopment	Immune function, inflammation, or disease	Gastrointestinal function; microbiome	Disease susceptibility; mortality	
Maternal cue	**Details**	**Putative route**	**Species**										**References**
Social	Social rank	Maternal androgens	Spotted hyena					✓					Dloniak et al. 2006
Social	Social environment stability	Maternal androgens	Guinea pig			✓[1,2]	✓[2,3]	✓[1,2,3]					Kaiser and Sachser, 1998[1], Kaiser et al., 2003[2], Kaiser and Sachser, 2001[3]
Social	Population density	Maternal androgens	Antarctic fur seal			✓							Meise et al. 2016
Maternal hormones	Androgen levels	Maternal androgens	Guinea pig		✓[1]			✓[2]					Brown-Grant and Sherwood, 1971[1], Phoenix et al. 1959[2]
Maternal hormones	Androgen levels	Maternal androgens	Marmoset		✓[1]			✓[2]					Huffman et al., 2017[1], Birnie et al., 2012[2]
Maternal hormones	Androgen levels	Maternal androgens	Ring-tailed lemur					✓					Grebe et al. 2019
Maternal hormones	Androgen levels	Maternal androgens	Rhesus macaque	✓[1]	✓[1,2,3]	✓[1,2,4]		✓[1,3]					Abbott et al., 2005[1], Herman et al. 2006[2], Goy et al., 1988[3], Abbott et al. 2008
Maternal hormones	Androgen levels	Maternal androgens	Mouse		✓[1]	✓[1,2]			✓[2]				Witham et al., 2012[1], Sullivan and Moenter, 2004[2]
Maternal hormones	Androgen levels	Maternal androgens	Rat		✓[1,2]	✓[2]		✓[1,2]	✓[3]				Rhees et al., 1997[1], Dela Cruz and Pereira, 2012[2], Simerly, 2002[3]
Photoperiod	Overnight light exposure	Maternal melatonin	Rat					✓[1,2]	✓[2]				Voiculescu et al. 2015[1], Voiculescu et al., 2016[2]
Photoperiod	Overnight light exposure	Maternal melatonin	Siberian hamster				✓[1]	✓[1]		✓[2,3]			Cissé et al., 2017a[1], Cissé et al., 2017b[2], Cissé et al. 2020[3]
Photoperiod	Day length	Maternal melatonin	Siberian hamster, Syrian hamster	✓[1]	✓[2,3]				✓[1]				Sáenz de Miera et al., 2017[1], Shaw and Goldman, 1995[2], Beery et al., 2008[3]
Photoperiod	Day length	Maternal melatonin	Guinea pig		✓[1,2]		✓[2]	✓[2]					Trillmich et al., 2009[1], Guenther & Trillmich 2013[2]
Photoperiod	Day length	Maternal melatonin	Meadow vole,	✓[1,2]	✓[1,2]			✓[3]					

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Table 1 (*continued*)

				Growth; metabolism; endocrine function	Timing of sexual maturation	Reproductive axis function; postnatal androgen levels	Stress axis function; postnatal glucocorticoid levels	Behavior	Neurodevelopment	Immune function, inflammation, or disease	Gastrointestinal function; microbiome	Disease susceptibility; mortality	
			montane vole										Horton, 1984[1], Lee and Zucker, 1988[2], Lee et al., 1987[3]
Photoperiod	Day length	Maternal melatonin	Red deer		✓	✓							Adam et al. 1994
Maternal hormones	Pinealectomy	Maternal melatonin	Siberian hamster					✓					Workman et al. 2008
Maternal hormones	Melatonin injections	Maternal melatonin	Siberian hamster		✓								Horton et al., 1989
Birth mode	C-section	Maternal microbiome	Human							✓[1]	✓[1-5]	✓[6]	Wampach et al., 2018[1], Grölund et al., 1999[2], Salminen et al., 2004[3]; Dominguez-Bello et al., 2010[4], Mueller et al. 2016[5], Sevelsted et al. 2015[6]
Nutrition	Juvenile coprophagy	Maternal microbiome	Koala								✓		Osawa et al. 1993
Nutrition	High fat diet	Maternal microbiome	Japanese macaque								✓		Ma et al. 2014
Nutrition	High fat diet	Maternal microbiome	Mouse							✓	✓	✓	Myles et al. 2013
Nutrition	Fiber	Maternal microbiome	Pig	✓							✓	✓	Cheng et al. 2018
Microbial manipulation	Probiotic[1], Antibiotic[2] or *E. coli*[2]	Maternal microbiome	Rat	✓[1]							✓[2]		O'Leary, 2019[1], Fåk et al., 2007[2]
Microbial manipulation	Bacterial treatment	Maternal microbiome	Mouse							✓[1]	✓[1]	✓[2]	De Agüero et al., 2016[1], Ibrahim et al., 2014[2]
Microbial manipulation	Germ free strain	Maternal microbiome	Mouse				✓[1]			✓[2]		✓[2]	Sudo et al., 2004[1], Olszak et al., 2012[2]
Microbial manipulation	Antibiotic	Maternal microbiome	Human									✓	Örtqvist et al. 2019
Stress	CVS[1], Fecal transplant[2], Restraint[3,4]	Maternal microbiome	Mouse	✓[2]			✓[2]	✓[3,4]	✓[3,4]	✓[1,4]	✓[3,4]	✓[1]	Jašarević et al., 2017[1], Jašarević et al., 2018[2]; Gur et al. 2017[3], 2019[4]
Social	Solitary, territorial species	Maternal microbiome	Red squirrel								✓		Ren et al. 2017
Social	Size of social/ care network	Maternal microbiome	Human								✓		Meehan et al. 2018
Maternal characteristics	Obesity	Maternal microbiome	Human								✓		Mueller et al. 2016
Maternal characteristics	Maternal quality/ condition	Maternal immune system	White-tailed deer	✓						✓		✓	Sams 1994

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Table 1 (*continued*)

				Growth; metabolism; endocrine function	Timing of sexual maturation	Reproductive axis function; postnatal androgen levels	Stress axis function; postnatal glucocorticoid levels	Behavior	Neurodevelopment	Immune function, inflammation, or disease	Gastrointestinal function; microbiome	Disease susceptibility; mortality	
Maternal characteristics	Maternal quality/ condition	Maternal immune system	Iberian red deer	✓									Landete-Castillejos et al. 2005
Immune manipulation	LPS	Maternal immune system	Rat					✓[4,5]	✓[1-5]	✓[1,2]			Cai et al., 2000[1], Urakubo et al., 2001[2], Bell and Hallenbeck, 2002[3], Basta-Kaim et al., 2012[4], Connors et al. 2014[5]
Immune manipulation	LPS and strain	Maternal immune system	Mouse					✓					Babri et al. 2014
Immune manipulation	LPS	Maternal immune system	Siberian hamster	✓			✓	✓					French et al. 2013
Immune manipulation	Poly(I:C)	Maternal immune system	Mouse	✓[5]				✓[1, 3-10]	✓[1,7,10]	✓[2,3,7]	✓[9]		Ito et al., 2010[1], Mandal et al., 2011[2], 2013[3], Malkova et al., 2012[4], Lins et al., 2018[5], Lins et al., 2019[6], Mueller et al., 2020[7], Berger et al., 2018[8], Hsiao et al., 2013[9], Ronovsky et al., 2017[10]
Immune manipulation	Poly(I:C)	Maternal immune system	Rat					✓[1,2]	✓[1]				Zuckerman and Weiner 2005[1], Missault et al. 2014[2]
Immune manipulation	Poly(I:C)	Maternal immune system	Rhesus macaque					✓[1-3]		✓[3]			Bauman et al., 2014[1], Machado et al., 2015[2], Rose et al., 2017[3]
Maternal disease	Classical swine fever	Maternal immune system	Wild boar									✓	Depner et al. 2000
Maternal disease	Vaccinia recombinant vaccine	Maternal immune system	Red fox									✓	Blasco et al. 2001
Maternal disease	Myxomatosis	Maternal immune system	European rabbit									✓	Fouchet et al. 2006
Maternal disease	Rabbit hemorrhagic disease virus	Maternal immune system	European rabbit							✓		✓	Robinson et al. 2002
Maternal infection	Infection and antibiotics	Maternal immune system	Human	✓									Li et al., 2020

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Table 1 (*continued*)

				Growth; metabolism; endocrine function	Timing of sexual maturation	Reproductive axis function; postnatal androgen levels	Stress axis function; postnatal glucocorticoid levels	Behavior	Neurodevelopment	Immune function, inflammation, or disease	Gastrointestinal function; microbiome	Disease susceptibility; mortality	
Nutrition	Obesity	Maternal immune system	Human							✓			Broadney et al. 2017
Nutrition	High fat diet	Maternal immune system	Rat							✓			Wijenayake et al. 2020
Nutrition	Protein malnutrition	Maternal immune system	White-tailed deer	✓[1]						✓[1,2]		✓[2]	Sams et al., 1995[1], 1996[2]
Nutrition	Low/High protein diet	Maternal immune system	Pig				✓			✓			Tuchscherer et al. 2012
Nutrition	Undernutrition	Maternal immune system	Sheep	✓						✓			Chadio et al. 2016
Maternal characteristics	Length of lactation	Maternal milk	Human	✓					✓				Rogan & Gladen 1993
Maternal characteristics	Length of lactation	Maternal milk	Mouse	✓			✓	✓					Rodríguez-González et al. 2020
Maternal characteristics	Length of lactation	Maternal milk	Guinea pig	✓	✓							✓	Künkele & Trillmich 1997
Maternal characteristics	Length of lactation	Maternal milk	Hooded seal	✓	✓				✓			✓	Schulz & Bowen 2004, Lydersen et al. 1995, Oftedal 2000, Lowe et al. 2017
Maternal characteristics	Length of lactation	Maternal milk	Brown hare, snowshoe hare	✓					✓			✓	Martinet & Demarne 1982, O'Donoghue & Bergman 1992
Maternal characteristics	Lactation stage	Maternal milk	Human	✓					✓	✓	✓		Kulski & Hartmann 1981, Hennet & Borsig 2016
Maternal characteristics	Breastfeeding vs Artificial feeding	Maternal milk	Human	✓[1]					✓[1-3]				Hoefer and Hardy, 1929[1], Rogan and Gladen, 1993[2], Bernard et al., 2013[3]
Maternal characteristics	Maternal milk vs donor milk	Maternal milk	Human	✓					✓				Hård et al., 2019
Maternal characteristics	Obesity	Maternal milk	Human	✓[1,2 4-7]					✓[1-4]	✓[3]		✓[1,2]	Dietz, 1997[1], Levin, 2000[2], Panagos et al., 2016[3], Ramos-Roman, 2018[4], Muhlhausler and Smith, 2009[5], Lukaszewski et al., 2013[6], Bautista et al., 2016[7]

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				Growth; metabolism; endocrine function	Timing of sexual maturation	Reproductive axis function; postnatal androgen levels	Stress axis function; postnatal glucocorticoid levels	Behavior	Neurodevelopment	Immune function, inflammation, or disease	Gastrointestinal function; microbiome	Disease susceptibility; mortality	
Maternal characteristics	Prematurity	Maternal milk	Human	✓									Hock et al. 2017
Nutrition	High fat diet	Maternal milk	Human	✓					✓	✓			Hernandez et al. 2012
Nutrition	High fat diet	Maternal milk	Rat	✓[1-3]			✓[1-3]	✓[1-3]	✓[1-4]	✓[1-4]			Bautista et al., 2016[1], Buonfiglio et al., 2016[2], Chen et al., 2017[3], Abuaish et al., 2020[4]
Nutrition	High fat diet	Maternal milk	Japanese macaque	✓				✓					Sullivan et al. 2010
Nutrition	Cafeteria diet	Maternal milk	Rat					✓	✓				Wright et al., 2011
Nutrition	Starvation	Maternal milk	Human	✓								✓	Painter et al., 2005
Nutrition	Low and high energy diets	Maternal milk	Rat	✓									Nicholas and Hartmann, 1991
Nutrition	MDE and miRNA deleted diets	Maternal milk	Mouse								✓		Zempleni et al. 2019
Maternal hormones	Cortisol/ Corticosterone	Maternal milk	Rat						✓				Zarrow et al. 1970
Maternal hormones	Cortisol/ Corticosterone	Maternal milk	Rhesus macaque					✓	✓	✓			Hinde & Capitanio 2010, Hinde et al. 2015, Dettmer et al. 2018
Maternal hormones	Cortisol/ Corticosterone	Maternal milk	Human	✓[1]				✓[2]				✓[1,3]	Painter et al., 2005[1], Grey et al., 2013[2], Hahn-Holbrook et al., 2016[3]
Maternal hormones	Leptin	Maternal milk	Human	✓								✓	O'Connor et al. 2003, Picó et al. 2007
Maternal hormones	Adiponectin	Maternal milk	Human							✓		✓	Jin et al. 2015, Lihn et al. 2005

on behavior. Finally, there can be within-species sex differences in the behavioral effects of prenatal androgens. In ring-tailed lemurs (*Lemur catta*) natural variation in maternal testosterone in late gestation is positively associated with female play behavior, but negatively associated with male play behavior (Grebe et al., 2019).

There is further evidence for the behavioral consequences of natural variation in maternal androgen levels if we consider anogenital distance and 2D:4D ratio as biomarkers of prenatal androgen exposure. Experimental work in rats, mice, and macaques (such as androgen treatment during gestation, androgen action disruption during gestation, or work with androgen insensitive strains) has shown that higher prenatal androgen exposure results in longer anogenital distances (Dean and Sharpe, 2013; van den Driesche et al., 2011). In multi-male groups of colobus monkeys (*Colobus angolensis ruwenzorii*), higher ranking males tend to have longer anogenital distances than lower ranking males (Teichroeb et al., 2020). Similarly, in wild house mice, male anogenital distance is positively associated with larger home range sizes and increased male dispersal (Drickamer, 1996). 2D:4D ratio has also been linked to prenatal androgen exposure, with a lower ratio (short second digit, long fourth digit) implying higher prenatal androgens, though some studies show conflicting results (Dean and Sharpe, 2013; Swift-Gallant et al., 2020). However, a recent study indicates that 2D:4D ratio may be tentatively linked with breeding strategy in primates. A comparison of 71 species of primates demonstrates that female 2D:4D ratio differs by female reproductive strategy, with monogamous species tending to have higher 2D:4D ratios (suggesting lower prenatal androgen exposure) than polygynous or polygamous species (Howlett and Wheeler, 2021).

HPG axis function is also altered in response to prenatal androgens in laboratory models (rats, mice, and macaques). These alterations can occur at multiple levels of the HPG axis. In mice, hypothalamic gonadotropin releasing hormone (GnRH) secretion is increased due to prenatal androgen-mediated increase of GABAergic signaling to GnRH neurons (Sullivan and Moenter, 2004). In macaques, prenatal androgens increase pituitary sensitivity to GnRH, resulting in increased luteinizing hormone (LH) levels (Abbott et al., 2008). There is also decreased sensitivity of the HPG axis to negative feedback (Abbott et al., 2008). Ultimately, prenatal androgen exposure in these species leads to higher androgen levels in adult female offspring and irregular estrous cycles (Abbott et al., 2008; Witham et al., 2012). Thus, prenatally androgenized animal models are used to study a phenotype similar to polycystic ovary syndrome (PCOS) in women, which is characterized by elevated circulating testosterone, irregular or absent menstrual cycles, and the development of polycystic ovaries (Abbott et al., 2008; 2005; Sullivan and Moenter, 2004).

Changes to the reproductive axis by prenatal androgens appear to affect reproductive life-history, but variation among species and studies makes it difficult to characterize the directional impact of these effects. Herman et al. (2006) hypothesized that because male puberty occurs later than female puberty in many mammals, prenatal androgen exposure should result in delayed female puberty as those females are "masculinized." This prediction holds true in macaques (Abbott et al., 2005). However, studies in marmosets (*Callithrix geoffroyi*) have found the reverse effect, where female sexual maturity is accelerated in offspring of mothers with higher androgen levels (Huffman et al., 2017). Studies in laboratory mice and rats have found both advancement and delay of female puberty in response to prenatal androgens (Abbott et al., 2005; Rhees et al., 1997; Sullivan and Moenter, 2004; Witham et al., 2012). As for male offspring, in rats and macaques, there is a negative relationship between prenatal androgens and offspring postnatal testosterone and puberty onset (Dela Cruz and Pereira, 2012; Herman et al., 2006). To further complicate these effects, in macaques, only androgen treatment in early gestation delayed female puberty, whereas treatment in late gestation had no effect, indicating the importance of species-specific timing of these cues and windows of developmental sensitivity (Abbott et al., 2005). Taken together, these studies indicate that prenatal androgen exposure may alter reproductive life history in a species- and sex-specific manner and could be a vector for programming of reproductive life-history during sensitive periods of development. Importantly, in these laboratory studies, it is possible that the experimental design (timing of androgen treatments, dosage, type of androgen used, laboratory housing and social conditions) may also contribute to inter-study differences.

2.2. Opportunities and outstanding questions

Investigations of the influence of prenatal androgens on fitness in natural mammalian systems are rare. Many studies in birds have related levels of maternal androgen deposition in eggs to environmental and social conditions and then to offspring traits (Groothuis et al., 2005; Hahn et al., 2017; Lipar and Ketterson, 2000). However, there have been very few ecologically relevant studies in mammals. Nevertheless, the laboratory evidence to date (and natural studies that have used proxies for prenatal androgens, e.g. anogenital distance) suggest that androgen-based programming of reproductive and behavioral characteristics and their fitness consequences should be a promising area of study. For example, androgens may program density-dependent adaptive phenotypes in mammals. Several studies in birds have found that androgen levels deposited in eggs vary by population densities (Groothuis et al., 2005), similar to the elevated maternal androgen levels documented in Antarctic fur seals in high density populations (Meise et al., 2016). This could be a promising mechanism for programming competitive behavior and reproductive physiology in high density environments, or in species with cyclic population dynamics.

An additional possibility is the role of prenatal androgen programming on male alternative reproductive tactics in species with resident and roaming males. Moore (1991) insinuated this relationship with the "relative plasticity hypothesis", which postulates that species that have fixed male alternative reproductive tactics must have these behaviors programmed in early life (organizational effects of androgens). Conversely, species that have plastic male reproductive tactics should have these changes mediated by differences in adult testosterone levels. There is evidence for the mediation of plastic reproductive strategies by fluctuations in adult testosterone levels (Schradin & Yuen 2011; African striped mice, *Rhabdomys pumilio*), but the programming of fixed male tactics has not been studied in mammals. If a particular reproductive strategy is adaptive under certain environmental conditions, and maternal androgen secretion is sensitive to environmental cues, strategy could be optimally programmed for the appropriate environment.

Some additional questions for prenatal androgens in natural populations include: 1) Do androgens act as a prenatal cue of the social environment in species where GCs do not fluctuate based on social status? 2) Are laboratory results that show changes in offspring HPG axis function and sexual maturation in response to maternal androgen treatment able to be replicated in a natural context, as a function of variation in maternal androgen levels? 3) What are the sensitive periods, or "programming windows" for androgen action on development in non-model species? These have been studied in rats and macaques (Goy et al. 1988, Welsh et al., 2008), but could be extrapolated more generally and could aid in reconciling differences between studies. 4) Are the findings of adaptive offspring phenotypes in response to maternal androgens seen in birds (deposited in eggs) generalizable to mammals?

3. Maternal melatonin

For many animals, the timing of life events is seasonal and circadian, and therefore depends on changes in photoperiod. Cues of the maternal photoperiod are largely transmitted to the fetus by melatonin, a hormone produced primarily by the pineal gland in the brain. Blood levels of melatonin peak overnight as pineal secretion is inhibited by light, via cues from the suprachiasmatic nucleus (SCN) of the hypothalamus in mammals (Jan et al., 2007; McCarthy et al., 2019). Though other organs

can also produce melatonin, they are not known to follow a circadian pattern and the melatonin is mostly retained locally instead of passing into circulation (Reiter et al., 2014). During gestation, circulating maternal melatonin is able to cross the placenta and influence the fetus (Klein 1972, Reppert et al. 1979, Reiter et al. 2014). Melatonin receptors are prevalent in fetal tissues including the brain, thyroid gland, gastrointestinal tract, and other organs (Thomas et al., 2002; Williams et al., 1997). However, the melatonin interacting with the fetus is primarily maternal in origin, as the neural circuitry of the SCN that drives circadian pineal secretion of melatonin does not mature until after birth (at least in humans; Jan et al., 2007). Thus, maternal melatonin is a critical cue for entraining fetal circadian rhythms (Jan et al., 2007; McCarthy et al., 2019; Varcoe et al., 2018).

3.1. Factors affecting maternal melatonin and impacts on offspring phenotype

Variation in melatonin cycles can be driven by differences in photoperiod (season and latitude) or by artificial disruptions to light and sleep cycle (e.g. women who work in overnight shifts and animals exposed to artificial light at night; (Le Tallec et al., 2016, Touitou et al. 2017). Though melatonin is key in establishing circadian rhythms, it also has a number of functions in fetal development. Embryonic cell proliferation is influenced by melatonin, and melatonin increases the developmental rate of mouse embryos *in vitro* (Ishizuka et al., 2000; Jan et al., 2007). Melatonin also acts as an antioxidant and free radical scavenger and thus protects maternal organs, the placenta, and fetus against reactive oxygen species during development (Jan et al., 2007; Reiter et al., 2014). Because of these protective properties, some studies in laboratory rats have examined maternal melatonin supplementation during pregnancy to ameliorate some of the negative programming effects of high fat diet and glucocorticoids. Maternal melatonin supplementation has been found to decrease offspring hypertension induced by high fat diet and high maternal glucocorticoid levels (in this case prenatal dexamethasone treatment; Tain et al. 2015).

The effects of melatonin on fetal development have led to speculation that melatonin may be a key timing cue in species that have highly synchronized births. Reindeer (*Rangifer tarandus*) have a very narrow calving period but variable gestation lengths, where females that mated earlier in the season have longer gestation periods than females mated later. It has been suggested that reindeer use photoperiod cues to adjust fetal developmental rate in order to calve simultaneously, and that this process is facilitated by the effects of melatonin on fetal development rate (Rowell and Shipka, 2009). Yet, other mechanistic possibilities exist for the role of the maternal photoperiod in timing of parturition. Maternal melatonin enhances oxytocin-induced contractility during labor in humans but has an inhibitory effect in rats, a difference that may facilitate the timing of births for the diurnal and nocturnal species, respectively (Ayar et al., 2001; McCarthy et al., 2019; Sharkey et al., 2009). Hence, there could be adaptations for seasonal timing of birth related to melatonin cues and the facilitation of parturition. However, this should only be applicable to species that evolved in a seasonal environment. In ungulate species living closer to the equator, where photoperiod is consistent throughout the year, timing of birth tends to be less synchronous than in the Northern temperate zones. Though, some equatorial species will still produce young synchronously, which in certain cases is thought to be adaptive for access to seasonal food resources or to offset chances of the young being consumed by predators ("predator satiation hypothesis"; Sinclair et al., 2000). For such species living near the equator, other environmental cues (such as rainfall) would be more important in the timing of birth and melatonin should not be linked to the onset of parturition (Ogutu et al., 2015; Sinclair et al., 2000).

In addition to physical effects of melatonin on the developing fetus, prenatal photoperiod has also been linked to altered behavioral phenotypes with clinical implications. Rats that were prenatally exposed to continuous maternal light performed poorly in memory tasks, showed more anxiety and depression-like behavior, and higher measures of neuronal oxidative stress (Voiculescu et al., 2016, 2015). Similarly, maternal pinealectomy increased depression-like behavior in Siberian hamster (*Phodopus sungorus*) offspring (Workman et al., 2008). In guinea pigs, offspring that gestate in a decreasing day length photoperiod (simulating fall) have reduced exploratory behavior than those that gestate in an increasing day length photoperiod (simulating spring; Guenther & Trillmich 2013). Disrupted circadian rhythms and melatonin secretion in adults are also associated with many psychiatric disorders, though the directionality of this relationship and whether it is susceptible to prenatal circadian influence are not known (Pacchierotti et al., 2001; Salgado-Delgado et al., 2011).

Maternal photoperiod and prenatal melatonin cues have ecological value in programming developmental and reproductive trajectories for the appropriate seasonal environment offspring will enter. Meadow voles (*Microtus pennsylvanicus*) that gestate in short day photoperiods (simulating winter) in the laboratory develop denser coats and build larger nests than those that gestate in long day photoperiods (Lee et al., 1987), though within-population genetic variation in photoperiod responsiveness in voles has been demonstrated (Spears and Clarke, 1988). The prenatal photoperiod also programs offspring thyroid stimulating hormone (TSH) sensitivity and thus influences postnatal metabolism in Siberian hamsters. Hamsters that experience a short day length *in utero* have increased TSH sensitivity of tanycyte cells in the hypothalamus, which ultimately regulate thyroid hormone levels (Sáenz de Miera et al., 2017). Photoperiod cues are also key for reproduction, which is seasonal in many species. Many rodents breed throughout the spring and summer and are reproductively quiescent over winter. Offspring born early in the breeding season may rapidly sexually mature, whereas offspring born late in the breeding season delay sexual maturation until the following spring. This season-dependent rate of sexual maturation can be programmed by maternal photoperiod *in utero*, with findings replicated in hamsters, voles, and guinea pigs (Beery et al., 2008; Horton, 2005; 1984; Lee and Zucker, 1988; Trillmich et al., 2009). A similar effect has been found in red deer (*Cervus elaphus*), where male offspring that gestated in long-day photoperiods had higher levels of luteinizing hormone, and an earlier increase in testosterone than those that had gestated in short-day photoperiods (Adam et al., 1994).

There is evidence that overnight shift work and light pollution (and the associated loss of the nocturnal melatonin peak) are associated with increased prevalence of several chronic illnesses (Navara and Nelson 2007, Torres-Farfan et al. 2020). However, there has been little study of the clinical impacts of prenatal effects on offspring (Varcoe et al., 2018). Studies of women working overnight shifts during pregnancy have addressed whether this increases the risk for pregnancy complications such as preterm delivery and preeclampsia, and have found little evidence suggesting that it does (Bonzini et al., 2011). Additionally, a study that examined the incidence of asthma, hay fever, and atopic dermatitis in children born to women who worked overnight shifts found no association between shift work and these diseases (Rada et al., 2020). Yet recent work in Siberian hamsters found maternal (and paternal) exposure to overnight dim light – even prior to conception – impaired offspring immune response to lipopolysaccharide (LPS; a bacterial/viral mimic) treatment (Cissé et al. 2020). Maternal exposure also decreased offspring swelling in response to a 2–4-dinitro-1-fluorobenzene (DNFB) challenge, but increased offspring antibody production to a novel antigen, indicating a suite of effects on offspring immune function (Cissé et al., 2017a). Importantly, parental exposure to light at night in these hamsters also resulted in decreased global methylation in the spleen of offspring, showing that there are epigenetic consequences of parental photoperiod (Cissé et al., 2017a). It is unclear whether these changes in hamsters in response to overnight light are applicable to humans or other mammals that evolved in completely different environments, or whether the changes are a generalizable artifact of altered melatonin secretion with applications across species.

3.2. Opportunities and outstanding questions

Many associations between maternal photoperiod, prenatal melatonin, and offspring postnatal disease remain untested. Due to the importance of maternal melatonin in fetal development, it has been suggested that future work should address whether preterm infants should be treated with melatonin to replace the essential maternal transfer that they would have received in late gestation (Jan et al., 2007). There is also an emerging link between parental photoperiod or overnight light exposure and the offspring immune system, and future work should continue to look into these clinical implications. This could also apply to disease susceptibility in natural populations. If increased maternal exposure to artificial night at light in urban and suburban areas may affect the developing immune system of offspring, they may have a differential response to pathogens. A promising model to examine this might be deermice (*Peromyscus maniculatus*), which are well-studied in terms of carrying disease and known to have some seasonal fluctuation in aspects of the immune system (Eleftheriou and Luis, 2020).

Because of the effects of prenatal photoperiod and melatonin on behavior described above, programming of offspring behavior in natural systems may be a worthwhile area of study. Work in Siberian hamsters, Syrian hamsters (*Mesocricetus auratus*), and California mice (*Peromyscus californicus*) has shown that exposure to either short day photoperiods or melatonin in adulthood alter aggression levels (Jasnow et al., 2002; Laredo et al., 2014; Munley et al., 2020; Silva et al., 2010). Maternal exposure to light at night in Siberian hamsters increases depressive behavior in offspring and decreases glucocorticoid receptor expression in the hippocampus, indicating both behavioral and stress-axis consequences (Cissé et al., 2017b). Whether prenatal photoperiod programs aggression and/or other behavioral differences in species where seasonal aggression is ecologically relevant is unknown.

Inter-population variation in photoperiod, that is, populations of the same species living at different latitudes, would also provide interesting insight into the effects of prenatal photoperiod on offspring phenotype. In species that are geographically widespread (for example, white-tailed deer, *Odocoileus virginianus*) offspring born in a more seasonal environment may show adaptive differences in growth rate, onset of reproductive maturation, and other elements of phenotype. However, studies would have to be carefully designed because populations would likely differ in other aspects aside from prenatal photoperiod (for example, primary productivity).

Another consideration is whether aspects of this seasonal programming apply to humans. While many animals rely on photoperiod cues to time reproduction, modern day humans do not appear to have such seasonal dependence. In a study compiling birth rates from several countries throughout periods of the 1900s, varying regional patterns were found (Lam and Miron, 1994). In the Southern United States and in India, there were strongly seasonal birth rates with lows in the early spring. The authors attributed this to lower rates of conception during the hot summer months, and perhaps lower access to air conditioning in some of these populations. Accordingly, in some of the Northern United States, Canada, and much of Western Europe, birth rates did not show as much seasonal fluctuation, and in Sweden they displayed the reverse pattern with a peak in spring (Lam and Miron, 1994). Whether early humans had seasonally-timed reproduction is not clear, nor if modern humans carry any evolutionary remnants of seasonal programming of behavior and physiology.

A final major question is whether artificial light at night will disrupt seasonal maternal programming effects in wild species. Artificial light at night is known to alter foraging behavior, affect predation risk, and influence migration patterns in many species (Navara and Nelson, 2007). It can also disrupt seasonal reproduction, causing timing of breeding to shift (Navara and Nelson, 2007, Robert et al. 2015, Le Tallec et al., 2016). Whether prenatal light cues will also create similar seasonal behavioral or reproductive mismatches in offspring has not been tested in wild mammals to our knowledge, but is a likely consequence of maternal exposure to artificial light at night.

4. Maternal microbiome

The holobiont concept considers individual animals and the millions to trillions of microorganisms that inhabit each of them as distinct host-microbe ecosystems (Zilber-Rosenberg and Rosenberg, 2008). The microbiome – the collective genome provided by the microorganisms living on and throughout the body – shows pronounced individual and inter-population variation, and is influenced by a variety of host and environmental factors (McFall-Ngai et al., 2013). The bacteria, archaea, protozoa, and viruses that make up an individual's microbial community regulate a number of functions essential to host health and physiology. These include immune, endocrine, and nervous system maturation and development, as well as metabolism, energy homeostasis, and behavior (Chung and Kasper, 2010; Cong et al., 2015; Ezenwa et al., 2012; Sampson and Mazmanian, 2015). Recent studies on the gut-brain axis have implicated the microbiome in neurodevelopment and behavior, including brain morphology (Luczynski et al. 2016), neurogenesis (Ogbonnaya et al. 2015), social recognition (Desbonnet et al. 2014), and anxiety-like behaviors (Heijtz et al. 2011, Messaoudi et al. 2011, Degroote et al. 2016). Furthermore, early life microbial variation is used as a predictor of later cognitive ability (Carlson et al., 2018). The microbiome can also play a number of ecological roles: increasing digestive efficiency and energy uptake from plant fibers and cellulose (Zhu et al., 2011), detoxifying plant secondary compounds (Kohl et al., 2014), defending against harmful pathogens (Hoyt et al., 2015), and contributing to the olfactory cues involved in chemical communication (Archie and Theis, 2011). These adaptations allow animals to exploit resources otherwise unavailable to them, decrease vulnerability to life-threatening diseases or infections, and mediate important social interactions such as kin recognition and mate choice. Thus, phenotypic variation in microbial community composition and function among individuals has the potential for marked fitness consequences in wild mammals (Suzuki, 2017).

4.1. Maternal microbial transmission

It is now widely accepted that maternal microbial transmission to offspring is universal across the animal kingdom (Funkhouser and Bordenstein, 2013). In mammals, there are two non-exclusive routes through which the maternal microbiome can act on developing offspring: *in utero*, and through vertical transmission at birth and in early postnatal life (Jašarević and Bale, 2019). Although the placental barrier was long thought to provide a sterile environment during gestation, studies have found maternal bacteria in amniotic fluid, umbilical cord blood, and the placenta, suggesting that infant microbial acquisition begins before birth (DiGiulio, 2012; Jiménez et al., 2005). Though the evidence for direct internal colonization has been debated (reviewed in Perez-Muñoz et al. 2017, Walker et al. 2017), there is another way in which the maternal microbiome can have prenatal effects. The gastrointestinal (GI) tract harbors the body's largest microbial assemblage and the products of its fermentation and metabolic activities contribute to the host's plasma biochemistry and circulating metabolites (Wikoff et al., 2009). Given that enzymes and nutrients can readily traverse the placental barrier (Nugent and Bale, 2015), compositional variation in the mother's gut microbiota can determine which metabolites and substrates are available for fetal provisioning in the womb, directly influencing rates of gestational growth and brain development in offspring (Lain and Catalano, 2007). At birth, offspring receive a crucial microbial inoculation from the mother's vaginal tract (Funkhouser and Bordenstein, 2013). Following this initial "bacterial baptism", maternal seeding of the offspring microbiome continues throughout the perinatal period via vertical transmission from her skin, mouth, breast milk, and (in some species) feces (Mueller et al., 2015). Infant microbial succession follows a fairly conserved age-related trajectory that is largely synchronized to the timing of dietary transitions (Koenig et al., 2011). In some species, juvenile coprophagic behavior (consumption of cecal

pellets and feces) allows for the acquisition of specially-adapted maternal microbes that will similarly ease the dietary transition from mother's milk to herbivory (e.g. Osawa et al. 1993, reviewed in Soave & Brand 1991). Thus, the neonate is initially colonized with maternal vaginal and skin strains, but these are progressively replaced by maternal gut strains (Ferretti et al., 2018; Jašarević et al., 2015), and eventually post-lactational dietary influences. For example, in humans the neonatal microbiome shows high individual diversity at birth, becomes increasingly complex across the first year of life (lactation and dietary influences), and then stabilizes and attains an adult-like configuration by approximately 3 years of age (Rodríguez et al., 2015; Yatsunenko et al., 2012).

Despite the growing influence of diet on the microbiome as individuals mature, a rapidly growing body of literature has made clear that the maternal microbiome can profoundly influence postnatal health and development, and that some of the effects on offspring phenotype are long-lasting (Mueller et al., 2015). To date the majority of this evidence stems from studies of humans and laboratory rodent models, however many of the factors shown to influence the maternal microbiome are relevant to – and may have similar impacts on – natural populations.

4.2. Factors shaping the maternal microbiome and impacts on offspring phenotype

The period immediately following birth is a critical window of "immune education" (see Section 5), whereby microbial colonization of offspring's mucosal and lymphoid tissues shapes immune system morphology and function (Eberl and Lochner, 2009; Gensollen et al., 2016). Studies of birth mode and maternal antibiotic use in humans offer insight into sub-optimal host-commensal interactions and provide evidence that disruption of these processes can have long-lasting impacts on health and disease susceptibility. Infants born via cesarean section have altered microbiota acquisition and development relative to vaginal births (Dominguez-Bello et al., 2010; Grölund et al., 1999; Salminen et al., 2004), weakened immunostimulatory potential (Wampach et al., 2018), and show increased incidence of chronic diseases (e.g. asthma, inflammatory bowel disease, arthritis, leukemia) in childhood (Sevelsted et al. 2015). A preliminary study has shown that swabbing cesarean-born babies with their mother's vaginal fluids immediately after birth – a practice known as "vaginal seeding" – can partially restore the infant microbiome (Dominguez-Bello et al. 2016), and several clinical trials currently underway are seeking to establish a causal link between vaginal microbiota transfer at birth and offspring health outcomes (e.g. clinicaltrials.gov, NCT03298334, NCT03567707). Similarly to birth mode, maternal antibiotic use during pregnancy is also associated with inflammatory bowel disease in offspring (Örtqvist et al., 2019). In rats, maternal exposure to a broad-spectrum antibiotic or *Escherichia coli* (*E. coli*) treatment during gestation and early lactation disrupts colonization of offspring's gut microflora, resulting in delayed stomach maturation and increased intestinal barrier permeability (Fåk et al., 2007). Transient microbial colonization of mice during pregnancy demonstrates that the maternal microbiome mediates innate immunity and epithelial development in offspring via induction of postnatal transcriptional activity in the small intestine, and that this programming depends on the transmission of maternal antibodies (De Agüero et al., 2016). Further, the absence of a microbiome in germ-free mice is associated with exaggerated hypothalamic–pituitaryadrenal (HPA) axis responses to an acute stressor (Sudo et al., 2004), and aberrant immune function leading to heightened mortality risk (Olszak et al., 2012). Interestingly, these studies found that the phenotypes generated could be rescued using bacterial re-colonization in early life, but not at later ages – highlighting developmental periods of sensitivity for healthy microbial establishment.

Whereas the above examples consider the impact of a complete absence or severe dysbiosis of the microbiome, intact maternal microbiomes also show natural variation as a function of host and environmental factors that can affect commensal community composition in offspring. Beyond providing the necessary nutritional building blocks for somatic growth in mammals, breast milk (see Section 6) also offers a continuous source of host-adapted microorganisms in early life (Cabrera-Rubio et al., 2012), as well as a variety of growth and immunomodulatory factors that regulate host-microbe interactions (Rautava, 2016). The microbial strains found in milk originate from maternal skin and GI tract sources (Demmelmair et al., 2020). Microbiota community composition and function are influenced by individual factors including maternal genetics, age, parity, health status, and birth mode (Gomez-Gallego et al., 2016; Zimmermann and Curtis, 2020), and the breast milk microbiome varies temporally as a function of lactational stage (Cabrera-Rubio et al., 2012) and maternal characteristics (Fitzstevens et al., 2017).

There is considerable cross talk between the endocrine and microbial systems, with reciprocal host-microbe production and response to hormonal signals (Neuman et al., 2015). Microbial diversity has been linked to individual measures of HPA axis activity in the wild (Stothart et al., 2019, 2016), with evidence for physical, psychological, and environmental stressors altering the gut microbiota. These alterations can have both positive and negative impacts on behavior, immunity, metabolism, and cognition (reviewed in Mackos et al. 2017, Karl et al. 2018). In turn, gut microbiota community assemblages may also mediate individual susceptibility to stress (Kentner et al., 2019a, 2019b). Thus, it is perhaps unsurprising that the microbiome has emerged as an early life regulator of HPA axis function (de Weerth, 2017; Foster et al., 2017). A series of studies by Jašarević and colleagues have interrogated the role of gestational stress in mother-offspring microbiome dynamics. They found that chronic variable stress exposure during the first week of pregnancy disrupts the murine vaginal microbiota across the entirety of gestation – an effect with likely repercussions on the maternal microbial transmission that occurs at birth (Jašarević et al., 2015). This prenatal stress paradigm results in compositional changes to the gut microbiota of male offspring at weaning (Jašarević et al., 2017), and alters the transcriptional activity of genes involved in GI development and intestinal immune function (Jašarević et al., 2018). Notably, transplantation of the microbiota from stressed mothers into naïve male offspring also recapitulates prenatal stress-mediated phenotypes (decreased body weight and heightened corticosterone responses to stress) in adulthood (Jašarević et al., 2018). Chronic restraint stress during pregnancy produces offspring alterations in the gut microbiota that last into adulthood in mice, accompanied by phenotypic effects on female anxiety-like behavior and neurotrophin expression in the amygdala (Gur et al. 2017), as well as altered male social interactions, oxytocin receptor expression, and biomarkers of inflammation in the brain (Gur et al. 2019). Taken together, these findings highlight the potential for long-lasting, stress-mediated modifications of offspring neurodevelopment.

Maternal nutrition during the perinatal period has actively been examined in the context of the developmental origins of disease as a contributing factor to offspring disease susceptibility (Chu et al., 2016). Several studies of maternal obesity during pregnancy and lactation suggest that a microbial mechanism of inheritance may be mediating those effects. Mueller et al. (2016) found that maternal obesity during pregnancy disrupts offspring microbiome acquisition at birth, and that this effect depends on exposure to the vaginal microbiome. A maternal high fat diet is responsible for alterations of the offspring microbiome in primate (Ma et al., 2014) and murine models (Myles et al., 2013), and in the latter these changes are associated with increased bacterial loads and mortality following infection, and disrupted immune responses. Interestingly, Myles et al. (2013) also found that postnatal administration of the same high fat diet to control-born offspring was insufficient to fully recapitulate the maternal diet effects, suggesting distinct routes of environmental influence (and developmental windows of susceptibility) on immune development. Maternal consumption of soluble fiber has similarly been shown to alter offspring gut microbiota composition. However, in contrast to the effects of dietary fat, increased maternal

fiber is associated with improved growth rates, reduced intestinal permeability, and enhanced disease resistance in piglets (Cheng et al. 2018). Though it appears that the composition or activity of the microbiome can, in some cases, compensate for changes in diet (Amato et al. 2014), the above data indicate that variation in resource availability or seasonal consumption patterns could alter the maternal microbiome and subsequent offspring phenotypes. The factors that affect resource acquisition and quality (territory selection or defense, foraging behavior) and interacting environmental influences such as predation risk (Lima & Dill 1990) thus represent additional sources of intra-individual variation and routes of maternal influence on offspring.

Recent research on sociality and the microbiome establishes its potential as an additional source of intra-individual variation for maternal programming effects. Given that social relationships mediate horizontal bacterial transmission among individuals (Archie and Tung, 2015), variation in social rank, behavioral phenotype, or behaviors that influence social interactions (e.g. the rates of allogrooming, number of mating partners, likelihood of dispersal) are likely mediators of the relative influence of maternal microbial transmission at birth. For example, maternal effects on offspring gut microbiomes are maintained into adulthood in a boreal forest population of solitary, territorial red squirrels (*Tamiasciurus hudsonicus)* (Ren et al. 2017), whereas Moeller et al. (2016) found little evidence of maternal effects in highly social eastern chimpanzees (*Pan troglodytes*), where the infant microbiome is shaped primarily by horizontal transmission and microbial diversity is homogeneous throughout the population. Nonetheless, rates of social interaction can still structure gut microbiome composition within social groups, as is seen in Welsh mountain ponies (*Equus ferus caballus*; Antwis et al. 2018) and in wild baboons (*Papio cynocephalus*), even when factors such as diet, kinship and shared habitat are taken into account (Tung et al., 2015). A similar effect is also seen in small-scale (hunter-gatherer, horticultural) human societies, where the composition and diversity of the maternal milk microbiome is related to the size of her social and cooperative infant care network (Meehan et al., 2018).

A final and underexplored topic in this field pertains to the potential influence of the microbiome on maternal care behavior. Individual variation in maternal care within and among litters can be heritable and has marked programming effects on offspring neurodevelopment and behavior (Pan et al. 2014). However, maternal behavior is also plastic and can be shaped by environmental and social factors, health, and previous experience (Palanza, 2017). Given the extensive interplay of the microbial, endocrine, and neurobehavioral systems (Cryan et al., 2019; Sylvia and Demas, 2018), and putative microbial influences on the availability of estrogen and oxytocin (Flores et al., 2012; Poutahidis et al., 2013; Varian et al., 2017), it is plausible that alterations of the maternal microbiome could result in care or behavior-mediated effects on offspring. Further, environmental influences on maternal behavior could also affect the degree of vertical bacterial transmission to offspring. Probiotic treatment during pregnancy and lactation in rats increases the frequency of maternal arched-back nursing, resulting in offspring that are heavier at weaning than those born to placebo mothers (O'Leary, 2019). Similarly, maternal inoculation with a single bacterial strain (*Lactobacillus reuteri*) during the perinatal period significantly increases maternal oxytocin levels and offspring fitness (survival to weaning) in mice, presumably as a function of oxytocin-mediated increases in maternal care (Ibrahim et al., 2014). Further experimentation will be necessary to determine the relative contribution of the maternal microbiome to maternal care behavior, but preliminary evidence suggests this is an avenue worth pursuing.

4.3. Opportunities and outstanding questions

The ultimate question for microbial programming studies in humans, laboratory models, and natural systems alike is whether variation in the maternal microbiome creates lasting phenotypic variation in offspring upon which natural selection can act (Suzuki, 2017). Studies of early life microbial acquisition and succession in wild systems will be critical to our understanding of the fitness consequences of microbiome-mediated programming effects (Amato, 2013; Suzuki, 2017). For example, a consideration of the role of the maternal microbiome could be particularly illuminating in ungulate systems characterized by asynchronous reproduction, such as in giraffes (*Giraffa camelopardalis*) where the seasonal timing of birth (wet versus dry season) is associated with both variation in dietary resource and differences in offspring survival (Lee et al. 2017). Captive microbiomes tend not to reflect those seen in natural populations (Hird, 2017), where hosts and microbiota have co-evolved over ecological time (but see Moeller et al. 2018). Transplantation of wild mouse microbiota into laboratory mice increases survival against infection (Rosshart et al., 2017), suggesting that wild microbiomes may constitute more representative models for complex human diseases. To date much of the evidence for maternally mediated microbiome effects is correlational, though the use of targeted antibiotic or probiotic treatments paired with assessments of fitness outcomes can help discern the functional significance of individual microorganisms or families. Priorities and outstanding questions for microbiome dynamics in natural populations include: 1) documenting the time course of microbial succession and periods of developmental susceptibility in wild mammals; 2) evaluating the relative influence of maternal, environmental, and host factors on microbiome composition and function across the lifespan, including sex-specific effects and host-microbiome genetic interactions (Stappenbeck & Virgin 2016); and 3) determining the relevant aspects of a species' natural history or individual characteristics that mediate susceptibility to these influences.

5. Maternal immune system

The mammalian neonatal immune system is shaped in the perinatal period, both *in utero* and after birth. At birth, offspring innate immunity is not fully developed, and thus susceptible to pathogens (Holt and Jones, 2000; Keller and Stiehm, 2000). During this period of immune immaturity, the survival of neonatal mammals critically depends on the acquisition and priming of innate and adaptive immunity from the mother for short-term protection against infections (Brambell, 1958; Koch et al., 2016; Zinkernagel, 2001). This form of passive offspring immunity is obtained via maternal antibody transfer, primarily of immunoglobulins (Igs) (Phillips, 1998). The method and timing of maternal immune transfer varies across mammalian species and can be greatly impacted by maternal condition and immunity.

5.1. Maternal immunity transmission

Maternal immunity is passively conferred to offspring by maternal antibody transfer via both the placenta and maternal milk. IgGs are the only class of immunoglobulin passed through the placenta from mother to fetus during gestation, through binding to Fc (fragment crystallizable) antibody receptors (Alberts et al., 2002; Malek et al., 1996). After birth, maternal milk is the main source of immune transmission, transferring Igs, cytokines, chemokines, macromolecules and immunologically bioactive components to the neonate (see Section 6; Molès et al. 2018). These components of milk act as anti-inflammatory, anti-microbial, and immunomodulatory agents to protect the offspring (Thibeau and D'Apolito, 2012). IgGs are also the primary Igs present in maternal milk during early postnatal life, with the highest levels found in the colostrum and early milk (Alberts et al., 2002; Molès et al., 2018). IgGs bind to Fc receptors in the GI tract of offspring, survive digestion, and can travel across the intestinal epithelium into central circulation (Alberts et al., 2002). IgAs facilitate neonatal immune maturation and help regulate the gut microbiome's bacterial composition (Mirpuri et al., 2013; Obata et al., 2010). This transfer facilitates offspring immune responses, aids with tissue repair and growth, and is involved in the overall regulation and development of the neonatal immune system (Molès et al., 2018; Thibeau and D'Apolito, 2012).

The developmental timing and extent of maternal immune transfer differs across species, and the primary method of transfer – gestational or lactational – depends on the species-specific structure of the placenta and the number of layers in the placental barrier (Chucri et al., 2010), along with the developmental trajectory and level of maternal care (Thibeau and D'Apolito, 2012). For example, in humans and other primates, rabbits, and guinea pigs, the majority of maternal immunity programming occurs during gestation through placental transfer of IgGs (Brambell, 1958; Phillips, 1998). In contrast, ruminants, horses, pigs, seals, and many carnivores receive much less placental transfer of maternal antibodies, and the majority of maternal immunity programming occurs through colostrum ingestion during the first 24 hours of life (Brambell, 1958; Chucri et al., 2010; Jeffcott, 1972; Marquez et al., 2003; Phillips, 1998). Species with low placental transfer are increasingly susceptible to neonatal infection than species with more placental transfer, as they depend greatly on colostrum ingestion in early life (Chucri et al., 2010). However, a select number of mammals gain maternal immunity intermediately from both the placenta and colostrum, including mice and rats (Brambell, 1958; Chucri et al., 2010). This maternally-derived immunity functions in the short term as young mammals begin to actively produce their own antibodies and develop acquired immunity (Brambell, 1958; Grindstaff et al., 2003). For example, maternally derived immunity to the Lagos bat virus and African henipavirus in fruit bat (*Eidolon helvum*) offspring lasted approximately 6 months, whereas acquired immunity lasted approximately 12 years and 4 years, respectively (Peel et al., 2018). In European rabbits (*Oryctolagus cuniculus*), maternal antibodies against the deadly myxomatosis disease are passed to offspring during gestation. When young are exposed during this period of maternal immunity, they experience mild symptoms and develop acquired immunity, reducing the impact of the disease in the population (Fouchet et al., 2006). Thus, maternal immunity transfer has important implications for offspring survival, but is not permanent and long-term immunity must be acquired by offspring through exposure or vaccination.

5.2. Factors shaping the maternal immune system and impacts on offspring phenotype

Given that offspring depend on the direct transmission of maternal antibodies, a sufficient level of IgG and other antibodies must be present in the mother's blood and milk at critical developmental timepoints for protective transmission to offspring to occur (Simister, 2003). Differential maternal antibody transmission can result from environmental conditions, such as nutritional resource availability, parasitic infections, environmental pathogens, and predation pressure (Grindstaff et al., 2003; Lazzaro and Little, 2009). This leads to differing physiological demands on the mother and variation in immune status that can drastically affect individual and offspring fitness (Lazzaro and Little, 2009). For example, in white-tailed deer, maternal immune status was strongly correlated with fawn survival in overpopulated herds (Sams, 1994). Varying maternal immune status and transfer can lead to genotypic and phenotypic variation in offspring, such as changes to brain development and behavior, which can be either advantageous or disadvantageous under certain conditions (Grindstaff et al., 2003; Spencer and Meyer 2017). A large concern to offspring development and disease is maternal immune activation and inflammation during gestation, particularly early in development (reviewed in Estes and McAllister, 2016; Spencer and Meyer 2017). There are many additional factors that contribute to maternal and fetal immune function, including maternal stress, nutrition, infection, trauma, and the microbiome (reviewed in Amarasekera et al. 2013, Marques et al. 2015, Macpherson et al. 2017).

The endocrine system, immune system, and the brain are closely linked, especially in regard to immune factors that impact neuroendocrine function. Maternal GCs are a major programming factor that can alter maternal immune transfer, as well as fetal immune development and response to pathogens. High levels of GCs act as an immunosuppressor and result in lower levels of maternal Ig production and reduced transfer of Igs to the developing offspring (Macpherson et al., 2017). High GCs during pregnancy can also lead to a down-regulation in the expression of the placental enzyme 11-beta-hydroxysteroid dehydrogenase 2 (Lesage et al., 2006; O'Donnell et al., 2012). The latter allows more maternal GCs and less maternal antibodies to reach the developing fetus; decreasing fetal growth, and leading to GC programming, altered HPA axes functioning, and altered immune status in the offspring (Lesage et al., 2006; Seckl, 1997). For example, in Australia, the survival of young European wild rabbits suffering hemorrhagic disease correlates to mother titer and depends on protective maternal antibody transfer (Robinson et al., 2002).

Along with high GCs, infection during gestation can hugely impact maternal antibody transfer. There is a large body of laboratory research on maternal immune activation from infection during gestation with varying neurodevelopmental effects on offspring (Careaga et al., 2017; Estes and McAllister, 2016; Harvey and Boksa, 2012; Kentner et al., 2019a). Basta-Kaim et al. (2012) exposed pregnant rats to LPS and found an increase in the levels of pro-inflammatory cytokines in male offspring at adulthood. Pregnant rats exposed to LPS also have increased proinflammatory cytokines in their amniotic fluid and placentas, as well as in the fetal brain, which indicates that some viral and bacterial infections can cross the placenta (Cai et al., 2000; Urakubo et al., 2001). In Siberian hamsters, maternal LPS exposure led to smaller litter sizes and offspring of both sexes having increased cortisol responses to stress (French et al., 2013). Further, maternal LPS exposure damages and decreases fetal white matter in the brain (Bell and Hallenbeck, 2002) and *in utero* exposure to polyinosinic:polycytidylic acid (poly(I:C); a viral mimic) in mice induces proinflammation and impairments in social behavior in offspring, that lasts into adulthood (Mueller et al., 2020), and modifies elements of both innate and adaptive immune systems (Mandal et al., 2013, 2011). Maternal poly(I:C) exposure is also associated with abnormal fetal brain development, size, and inflammation (Fatemi et al., 2002), and behavioral abnormalities (Lins et al., 2019; 2018; Mandal et al., 2013), similar to schizophrenia (Ito et al., 2010; Zuckerman and Weiner 2005) and autism spectrum disorder (Malkova et al., 2012) in humans. There has also been significant research of maternal immune activation with Poly(I:C) on rhesus macaques showing offspring with long-term immune activation, and behavioral changes resembling those of autism and schizophrenia, such as increased repetitive behaviors and low eye fixation (Bauman et al., 2014; Machado et al., 2015; Rose et al., 2017).

Maternal infection can act as a disease primer, which affects offspring outcome, including brain and behavioral changes through the maternal immune response (Careaga et al., 2017; Estes and McAllister, 2016). The laboratory literature has demonstrated the importance of type, severity, and timing of infection in offspring behavioral phenotypes (Careaga et al., 2017; Kentner et al., 2019a, 2019b). Additionally, offspring born to mothers with infection have altered microbiota signatures at birth and GI barrier defects, which can lead to behavioral defects (Hsiao et al., 2013; see Section 4). In humans, antibiotic use during pregnancy and birth, particularly for group B streptococcus positive women is thought to lead to obesity in offspring. There is limited evidence for these effects; antibiotics have been shown to alter the infant microbiome (Section 4), and it is untreated infection itself that has been shown to lead to childhood obesity and impacted maternal and offspring microbiome (Li et al., 2020; Seedat et al., 2017). Furthermore, maternal immune activation from Poly(I:C) in mice led to abnormal maternal care behavior and increased depression-like behavior in female F1 offspring (Berger et al., 2018; Ronovsky et al., 2017). Maternal immune activation has transgenerational effects in offspring brain development, behavioral abnormalities, and disease risk (reviewed in Pollak and Weber-Stadlbauer 2020). Worth considering is that many of these laboratory studies are exposing naïve females to antigens and infections while pregnant, whereas in wild populations, natural exposure and immunological memory could occur prior to pregnancy. The laboratory

literature highlights the immense complexity in alterations to offspring development and phenotype due to maternal immune state, however knowing and quantifying antibodies and antigen exposure of wild animals can be problematic (as outlined in Boulinier and Staszewski 2008).

Maternal nutrition during critical perinatal periods also shapes the development of the fetal and neonatal immune system (Amarasekera et al., 2013; West et al., 2010). Maternal overnutrition that results in obesity is characterized by chronic inflammation and programming effects on the mother and offspring (reviewed in Heerwagen et al. 2010). In humans, obese mothers give birth to newborns with increased IgM and proinflammatory profiles (Broadney et al., 2017) – both of which are signals of poor immune function. Further, exposure to a diet rich in saturated fats during gestation and lactation, leads to sex-specific immune programming in offspring, where adult male offspring exhibit enhanced proinflammation, and adult female offspring exhibit enhanced anti-inflammation in response to LPS and corticosterone challenges (Wijenayake et al., 2020). Though obesity is not a common condition in wild mammals, resource acquisition (and thus individual nutrition and quality) can depend greatly on internal and external factors such as fitness, rank, territoriality, predation, and more. In Iberian red deer (*Cervus elaphus hispanicus*), high quality mothers (experienced, larger body size) have greater milk production, increased levels of milk Igs and more rapidly growing fawns (Landete-Castillejos et al., 2005). Interestingly, in Chinese painted quail (*Coturnix chinensis*), the amount of antibody transferred from mother to offspring was related to maternal condition, and not the mother's immune response (Coakley et al., 2014).

Moreover, further studies are needed to characterize maternal and offspring immune status as a function of nutritional state in wildlife populations, when compared to urban populations that are exposed to poor-quality anthropogenic food sources that are low in protein and high in saturated fats. Van Heugten et al., (1996) and Maggini et al., (2007) reported that consumption of poor-quality anthropogenic foods by wild populations living in urban areas could lead to impaired antibody-mediated immune function with transgenerational effects. Similar immune effects have been reported in wild populations living in rural areas, where supplemental feeding of rock iguanas (*Cyclura nubile*) by tourists in the Bahamas with carbohydrate-rich foods such as grapes and cereal, was associated with increased hookworm (*Ancylostoma duodenale*) burden (Knapp et al., 2013). Southern stingrays (*Dasyatis americana*) fed by boat operators and tourists in the Cayman Islands also experienced notable impairments in immune status (Semeniuk et al., 2009). Nevertheless, alternate studies have reported immune advantages of wild populations consuming a novel urban diet, where urban kit foxes (*Vulpes macrotis*) living in residential areas in California had better immune status compared to exurban kitfoxes, likely due to the improved access to water and food (Cypher and Frost, 1999). However, further research is needed to delineate the developmental programing consequences of wild populations consuming a novel urban diet and its association with immune programing of offspring.

Maternal undernutrition, specifically protein limitation, can also affect the transfer of maternal antibodies during gestation and lactation, in part due to higher levels of circulating GCs (Macpherson et al., 2017; Sams, 1994). Undernutrition can lead to lower expression of Fc receptors in the placenta, and less maternal antibodies passing from the mother to the fetus during gestation (Kearney et al., 2015; Macpherson et al., 2017). Protein malnutrition during pregnancy can lead to higher neonatal mortality, lower Ig levels, higher cortisol responses to stress, and delayed body mass gain in surviving offspring (Sams, 1994; Sams et al., 1996; Tuchscherer et al., 2012). However, studies attempting to artificially mimic wild conditions of malnourishment and low protein availability during pregnancy were not able to recreate these chronic conditions; mothers did not have decreased colostrum Ig levels, and offspring failed to display compromised immunocompetence (Chadio et al., 2016; Sams et al., 1995). This suggests that lactating mothers may be able to break down protein reserves during times of nutritional limitation in order to support milk production and maintain immune protein concentration in the milk (Pine et al., 1994; Sams et al., 1995). This demonstrates the extreme variability of the effects of over- and under-nutrition on mothers and offspring as a function of varying environmental conditions, however further study of additional species and conditions is required.

5.3. Opportunities and outstanding questions

Whereas immunology is intensively studied in laboratory models under controlled conditions, those findings do not easily translate to wild mammals in natural environments. Even within laboratory conditions, there are large differences in maternal reaction to immune activation during gestation (Missault et al. 2014), and differences in offspring outcome between mice strains (Babri et al. 2014). Wild mice and rats carry a higher burden of infections and have higher serum IgG and IgE than laboratory counterparts (Abolins et al., 2017; Devalapalli et al., 2006). Wild mice are genetically and immunologically different from laboratory mice (Abolins et al., 2017; Viney et al., 2015), and extensive variation in immune phenotypes are seen between neighboring wild populations (Abolins et al., 2018). Additionally, the habitat and environment of adult wild rats has the largest effect on Ig levels, more so than age or sex (Devalapalli et al., 2006). In a laboratory study, the negative effects to the HPA axis and social behavior from maternal immune activation was alleviated in juvenile male rats by environmental enrichment during and after gestation (Connors et al. 2014). These findings highlight how laboratory studies may differ from wild populations, as environmental conditions and natural selection could act to limit many phenotypes. Thus, we must exercise caution in extrapolating findings from laboratory studies to wild species.

The immune state, antigen load, and antibody transfer to offspring of many adult wild mammals is simply unknown and difficult to quantify (Boulinier and Staszewski 2008). Nonetheless, research looking at potential programming effects of maternal immunity on offspring development can help guide our understanding of wildlife infection and disease ecology. For example, wild boar piglets (*Sus scrofa*) were protected by maternal antibodies against classical swine fever when exposed at 3 months old (Depner et al. 2000). Also, in captive red foxes (*Vulpes vulpes*), maternal rabies neutralizing antibodies were passed from vaccinated mothers to offspring, but protective titers were decreased by 45–75 days after birth (Blasco et al., 2001). Further research on maternity antibody transfer could be beneficial in research on epizootics and wildlife vaccination programs.

Factors that affect maternal immunity and the associated offspring phenotypes are well characterized in model species, yet some of the intermediate physiological and developmental steps of maternal immune transmission need elucidation in wild systems (Grindstaff et al., 2003). In particular, information is lacking for non-model systems, particularly in terms of the source, timing, amount, and strategies of maternal antibody transfer, as well as the critical windows of developmental sensitivity across species (Boulinier and Staszewski 2008). Worth considering in wild mammal immunity research is the potential for tradeoffs between current investment in maternal antibody transfer and future reproductive events (Boulinier and Staszewski 2008). Further investigations of the short- and long-term effects of alterations in maternal immune function on offspring in the wild are warranted, as are the longer-term epigenetic and evolutionary effects on individuals and populations.

6. Maternal milk

Maternal milk is the primary nutritional source of all newborn mammals, but it is also a principal factor in early life programming that can induce later life effects (Melnik & Schmitz 2017, Boquien 2018, Victora et al., 2016). Milk consists of a variety of complex macro and micronutrients, including fatty acids, protein, carbohydrates, vitamins, minerals, as well as non-nutritional, bioactive compounds (Andreas

et al., 2015; Ballard and Morrow, 2013). Some of the well-characterized bioactive compounds of milk include: 1) hormones, such as leptin, prolactin, adiponectin, calcitonin, somatostatin, resistin, and ghrelin (Ballard and Morrow, 2013); 2) growth factors, such as epidermal growth factor, neuronal growth factors (brain-derived neurotrophic factor), and insulin-like growth factors (Ramos-Roman, 2018; Young et al., 2017); 3) oligosaccharides (Newburg et al., 2005); 4) female reproductive hormones, including estradiol (E2), estriol (E3), and progesterone, 5) hypothalamic peptide hormones, including GnRH (see Section 2), luteinizing hormone-releasing hormone, and thyrotropin-releasing hormone (Baram et al., 1977; Amarant et al., 1982; Lu et al., 2017), 6) a complex microbiota (see Section 4, De Leoz et al., 2015), and 7) immune components, including Igs, cytokines, and chemokines (see Section 5, Molès et al., 2018).

6.1. Milk composition and transmission

6.1.1. Species-specific lactation curves

Maternal milk is highly dynamic and is tailored to meet the nutrient, developmental, and immune demands of the offspring as they age. As such, maternal milk composition varies widely across species, lactation age (Andreas et al., 2015; Boquien, 2018; Kulski and Hartmann, 1981; McCutcheon and Marinelli, 2009; Skibiel et al., 2013), circadian cycle, and even within a single feed, where notable differences between foremilk and hindmilk composition has been reported (Andreas et al., 2015; Ballard & Morrow, 2013; McGuire et al., 2021). For example, total milk fatty acid content can vary from 0.2% in black rhinoceros (*Diceros bicornis*), to 3–5% in humans, to 60% in some species of true seals (Iverson and Oftedal, 1995). Moreover, maternal milk is typically richer in fatty acids, protein, and energy content in carnivorous than in herbivorous species (Skibiel et al., 2013).

Milk composition also varies by stage of lactation in most placental and marsupial mammals. The variability in lactation stages across species stems from the fact that mammals are born at different stages of development, are suckled for different lengths of time, and weaned at different stages (Bozzano, 1995). Further, the length of lactation/feeding greatly affects developmental programming of offspring across mammals, with the largest impact reported in humans and laboratory rodents (Rodríguez-González et al., 2020; Rogan and Gladen, 1993). Length of lactation is typically longer in altricial mammals than in precocial, yet precocial primates have an extended lactation stage compared to precocial rodents, due to a variety of selection pressures, including reproductive interval, length of gestation, rate of attaining adult body mass, litter size, and age at first parturition (Derrickson, 1992). Interestingly, the peak energy demand during lactation on mothers with precocial offspring (i.e. guinea pigs) is reported to be lower than that of mothers with altricial offspring mainly because the pups in the former receive a substantial portion of the required nutrients through solid food intake (Künkele and Trillmich, 1997). However, a notable exception is true seals (*Phocidae*), who give birth to large precocious pups and have a very short lactation period of 4–5 days (hooded seals (*Cystophora cristata*); Schulz & Bowen 2004). During lactation, true seal mothers suffer dramatic losses in body mass while transferring reserves rich in macro/micronutrients to offspring. This feeding behavior result in a daily doubling of pup body mass and increased development (Lowe et al., 2017; Lydersen et al., 1995; Oftedal, 2000). The evolutionary advantage of this abbreviated yet metabolically demanding lactation period on the mother is not clear, however, this strategy expedites postnatal development and maturation of offspring (Lowe et al., 2017; Oftedal, 2000) and allow them to forage for food and reach independence earlier.

In modern day humans, the lactation period and the length of breastfeeding depends on cultural, geographical, health, and socioeconomic factors, but typically lasts 6 to 12 months with three stages. Stage 1) colostrum (postnatal day (PND) 0–5) is rich in immunological components including IgA, lactoferrin, leukocytes, and developmental factors such as epidermal growth factor, and contains very low levels of lactose. Thus, the primary function of colostrum is immunological rather than nutritional (Lee and Kelleher, 2016). Colostrum plays a vital role in the development of offspring immunity and the microbiome soon after birth. Stage 2) transition milk (PND5 – 14), has some immune and mineral properties, but contains high levels of lactose and other macromolecules to meet the nutrient and energy demands of the growing offspring (Kulski and Hartmann, 1981). Stage 3) mature milk, the final stage of human lactation curve, has a high lipid and casein content and about half the amount of oligosaccharides, compared to colostrum and transition milk (Hennet and Borsig, 2016). Mature milk is designed to prepare the infants for a smooth transition between exclusive milk feeding to other nutritional sources. Nevertheless, the length of lactation and breastfeeding duration varies largely across human mothers even with similar socioeconomic and cultural backgrounds. Importantly, this variability can lead to altered physiological and cognitive development in offspring. Specifically, Rogan and Gladen (1993) were one of the first to report enhanced cognitive development in exclusively breastfed middle class, Caucasian children from 2 to 5 years of age, compared to those that were on infant formula (Rogan and Gladen, 1993). Bernard et al., 2013 reported a similar finding in the French EDEN mother–child cohort study, where longer breastfeeding duration was positively associated with better cognitive and motor development in 2- and 3-year-old children (Bernard et al., 2013).

Seasonal variation in lactation curves in mammals can also lead to altered developmental outcomes in offspring. Brown hares (*Lepus europaeus*) and snowshoe hares *(L. americanus)*, which give birth to highly precocial leverets, lactate for short and infrequent periods (once a day for 25 to 28 days) and have highly concentrated milk (Martinet and Demarne, 1982). However, leverets from the last litter of the season may be nursed longer, which can enhance their survival during fall and winter months (O'Donoghue and Bergman, 1992). Similarly, the lactation curves in other mammals differ according to their natural history and the growth trajectories/requirements of the offspring (Lowe et al., 2017). Therefore, when conducting cross-species milk analysis it is important to take the stage of lactation into account, as interspecific differences may be confounded by intraspecific variation and lead to erroneous conclusions, especially in natural populations.

6.1.2. A new player: milk-derived exosomes and milk miRNAs

Maternal milk contains a plethora of non-nutritive, bioactive components. Milk-derived extracellular vesicles (EVs) are one of the most abundant bioactive components of mammalian milk and can be categorized into three groups based on their size, biogenesis, and cargo. Exosomes are the smallest EVs discovered to date (30–150 nm) and are formed via endocytic pathway (Melnik et al., 2016; Melnik and Schmitz, 2017; Zempleni et al., 2019). Milk-derived exosomes (MDEs) contain a protective lipid outer layer that can withstand gastrointestinal digestion (Pieters et al., 2015), RNases and protease treatments, and changes in temperature (Howard et al., 2015). MDEs have been discovered and quantified in humans (Ballard and Morrow, 2013; Boquien, 2018; Hock et al., 2017; Zempleni et al., 2017; Zhou et al., 2012), cows (Izumi et al., 2015, 2012), pigs (Chen et al., 2014; Gu et al., 2012; Lin et al., 2020), rodents (Izumi et al., 2014), and marsupials (Modepalli et al., 2014), and are abundant across fractions of milk and across lactation stages (Alsaweed et al., 2015b; 2015a; Munch et al., 2013).

MDEs contain microRNA (miRNA), messenger RNA (mRNA), lipids, and peptides that may play important roles in cell-to-cell communication, metabolism, immunity, intestinal growth, as well as gene expression in the recipient (Zempleni et al., 2019). For example, rat MDEs promote intestinal epithelial cell viability and proliferation, and stimulate intestinal stem cell activity during early-postnatal life (Hock et al., 2017). Notably, MDEs are also implicated in the regulation of the offspring gut microbiome (see Section 4), where consumption of a MDE and RNA depleted diet lead to a notable decrease in microbiome complexity in mice (Zempleni et al., 2019).

Milk miRNAs, encapsulated in MDEs, are short (17–22 nucleotides) non-coding RNAs that regulate gene silencing via post-transcriptional regulation of target mRNA (Alvarez-Erviti et al., 2011; Gebert and MacRae, 2019). Milk miRNAs primarily originate from the mother's mammary gland epithelial cells and are likely exogenous in origin to the offspring (Alsaweed et al., 2016; Melnik et al., 2016). More than 300 unique milk miRNAs have been discovered in human milk and more than 9,000 potential mRNA targets with complementary 3′-untranslated regions (UTR) are predicted to exist (Munch et al., 2013). As such, milk miRNAs may mediate post-transcriptional regulation of various mRNA targets in recipient tissues (Baier et al., 2014; Benmoussa and Provost, 2019; Chen et al., 2014; Izumi et al., 2015; Manca et al., 2018). Further, relative to other taxa, the human GI tract is largely underdeveloped in early postnatal life, and maternal milk is responsible for orchestrating its development and maturation (Montgomery et al., 1999). This allows for a larger migration of MDEs across the intestinal epithelium into the central circulation (Gu et al., 2012) and increased milk miRNA bioavailability in offspring tissues (Zempleni et al., 2017), including the brain (Chen et al. 2016, Manca et al. 2018). Therefore, milk miRNA may not only regulate transcriptional output of the mammary glands but may also be involved in early-life posttranscriptional programming of offspring (Abuaish et al., 2020; Alsaweed et al., 2015a; Baier et al., 2014).

6.2. *Maternal factors shaping milk composition and impacts on offspring phenotype*

Milk composition is highly sensitive to maternal diet and psychosocial stress in humans and laboratory rodents (Bautista et al., 2016; Hernandez et al., 2012; Panagos et al., 2016; Purcell et al., 2011; Ramos-Roman, 2018). Changes in milk composition as a direct result of changes in maternal diet (overnutrition or undernutrition) lead to irregular metabolic imprinting of offspring (Bautista et al., 2016; Buonfiglio et al., 2016; Chen et al., 2017; Hernandez et al., 2012). Metabolic imprinting is a process whereby a metabolic stimulus or an insult occurring during a critical developmental period imposes a life-long effect on the offspring (Waterland and Garza, 1999). Indeed, a higher tendency to gain body weight, increased visceral fat deposition, increased proinflammation, and development of metabolic disorders during adulthood can be traced back to alterations in milk composition as a function of maternal diet (Dietz, 1997; Levin, 2000; Park, 2005). In particular, maternal obesogenic diets reduce the total milk yield, the carbohydrate and omega-3 fatty acid content in milk, and are associated with lower brain weight and impaired neurodevelopment in offspring (Bautista et al., 2016).

Changes in milk composition due to maternal diet and other environmental exposures, including immune and psychosocial stress, also contribute to postnatal programming of neuronal circuits, fat-cell number (Ramos-Roman, 2018), adipose tissue mass and function (Lukaszewski et al., 2013; Muhlhausler and Smith, 2009), and metabolic response to key energy hormones (including leptin, adiponectin, and insulin) in offspring. Leptin regulates neonatal energy balance, adiposity, and physiological development (Sánchez et al., 2005). Interestingly, infants who receive optimal levels of milk leptin are more resistant to fat accumulation and adiposity in adult life than infants fed with formula that lacks leptin (O'Connor et al., 2003; Picó et al., 2007). Further, breast fed infants nursed by obese mothers have higher levels of leptin than infants nursed by lean mothers (Bautista et al., 2016). This suggests that there is an optimal concentration of leptin in milk and that deviations from this optimal range due to changes in maternal diet may disrupt early-life programming and result in long-lasting metabolic alterations in offspring. Similarly, high and low levels of adiponectin, another important energy hormone in milk that regulates plasma glucose, as well as fatty acid breakdown, enhance neonatal inflammation (Jin et al., 2015), and place offspring at risk of later-life metabolic disorders, including type II diabetes (Lihn et al., 2005).

Diet is also one of the main maternal cues that influence the concentration of female hormones in breast milk, including E2, E3, and progesterone (Jiang et al., 2016a; Jiang et al., 2016b). Lu et al. (2017) reported in a human cohort with 32 lactating mothers from Hangzhou, China, the level of E3 and progesterone in the milk was significantly associated with maternal diets rich in protein (particularly meat and eggs) and the E2, E3, and progesterone concentrations varied largely across lactating period from colostrum, to transition milk, and mature milk.

Further, maternal diet is closely associated with maternal lactation and care behavior during early postnatal development (Abuaish and McGowan, 2017). Purcell et al., (2011) found that laboratory rat dams that were on a high fat diet during gestation and lactation spent more time nursing their pups during the first postnatal week and offspring exposed to a maternal high fat diet consumed more milk compared to the control counterparts. Rodent dams that were on a high fat diet also spent more time blanket nursing compared to the control dams during the dark phase of the circadian cycle (Abuaish et al., 2018). The authors postulate this to be a compensatory lactation behavior employed by rodent mothers to combat impairments in lactation that is often associated with high fat diet consumption. Similarly, an earlier study reported that rodent dams on a high fat and protein supplemented diet exhibit increased postural nursing, pup grooming, and spent more time attending to the pups compared to the control dams (Bertino, 1982). Alternatively, Frankova (1971) reported notable impairments in maternal behavior in rat dams that were fed a low protein and high carbohydrate diet, where mothers took a longer time to locate and retrieve scattered offspring and initiate nursing. These differences in behavior in laboratory models illustrates that maternal diet shape maternal care behavior during key stages of early-development.

Maternal milk is also a rich source of GCs (Grosvenor et al., 1993; Hamosh, 2001; Stead et al., 2021). GCs play a critical role in early life programming through transmission of stress hormones and enhanced proinflammatory markers across mother-offspring dyads via the placenta *in utero* and via maternal milk during postnatal life (Bertram and Hanson, 2002; Welberg and Seckl, 2001). GCs are highly sensitive to changes in maternal diet and perinatal exposure to diets rich in saturated fats increase basal levels of plasma GCs in laboratory rat offspring (Abuaish and McGowan, 2017; Sasaki et al., 2014, 2013). However, the association between milk GCs and their influence on offspring development, behavioral patterns, and immune function warrants further investigation. Nevertheless, studies in laboratory rats have shown that maternal milk GCs are readily transported across the intestinal epithelium and are present in detectable amounts in the offspring plasma as well as the brain (Zarrow et al., 1970). Furthermore, increased milk cortisol transfer programs metabolic functioning and reduces childhood obesity risk in humans (Hahn-Holbrook et al., 2016). Cortisol concentrations in milk are also associated with impulsivity, cognitive ability, social behavior, and development of temperament in rhesus macaques (Dettmer et al., 2018; Hinde et al., 2015; Hinde and Capitanio, 2010). Taken together, these studies suggest that variation in maternal milk GCs in response to nutrient stress may induce alterations in offspring behavior, immune responses, development, cognitive, emotional, and social adaptations (Abuaish and McGowan, 2017; Hechler et al., 2018; Painter et al., 2005; Sullivan et al., 2010; Wijenayake et al., 2020; Wright et al., 2011).

Milk also contains milk miRNAs that contribute to the establishment of offspring immunity (Zhou et al., 2012), the microbiome (Doare et al., 2018), the transcriptome and the epigenome (Chen et al., 2010; Golan-Gerstl et al., 2017; Izumi et al., 2014). Similar to other components of milk, milk miRNA is sensitive to maternal cues (Abuaish et al., 2020). miR-148/152 family, miR-29 family, and miR-21 are of particular importance because they link the mother's lactation genome to epigenetic programming of her offspring (Melnik and Schmitz, 2017). These milk miRNAs are known regulators of DNA methyltransferases (DNMTs) (Benmoussa and Provost, 2019; Duursma et al., 2008; Fabbri et al., 2007; Pan et al., 2010), the enzymes that catalyze DNA 5-methylcytosine (5mC) modifications (Long et al., 2014; Wang et al., 2014). Thus, they play vital roles in regulating CpG methylation and subsequent

transcriptional outcome of target gene promoters. DNMTs (DNMT1, DNMT3a, DNMT3b, and DNMT3L) are key transcriptional regulators that are vital parts of somatic, germline, and embryonic cell development as well as genomic immunity,mammalian development, and disease regulation (Bender, 2004; Greenberg and Bourc'his, 2019; Jin et al., 2011). Interestingly, offspring exposed to a maternal diet rich in saturated fats during perinatal life showed reduced abundance of miR-148/152 and miR-21 in ingested stomach milk and in the brain (amygdala) and this reduction was strongly associated with increased DNA methylation during early life (Abuaish et al., 2020). This study illustrated two important findings: first, that milk miRNAs are potentially crossing the blood brain barrier during early postnatal development and second, that milk miRNAs may help program the offspring's epigenome in response to maternal nutritional stress. In addition to regulating DNMT expression, milk miRNAs also impose extensive transcriptional regulation on developmental genes in the offspring via DNA CpG demethylation, including fat mass- and obesity-associated protein (Adhikari et al., 2016; Wu et al., 2016). Milk miRNAs also regulate the expression of two master transcription factors, FOXP3 and nuclear factor kappa B, that mediate T-cell function and regulate pro/anti-inflammation, respectively (Ouni et al., 2015). Milk miRNAs also target rapamycin complex 1 (Melnik et al., 2013), a critical nutrient sensing kinase that controls protein translation, cell proliferation/differentiation, and the function of insulin-like growth factor 1, a vital hormone that controls postnatal growth (Ouni et al., 2015). Taken together, these studies show that milk miRNAs not only program the offspring epigenome but may also play an important role in developmental and immune programming. A detailed description of these developmental targets and an in-depth description of the modes of action can be found elsewhere (Melnik et al., 2016; Melnik and Schmitz, 2017; Zempleni et al., 2019).

6.3. *Opportunities and outstanding questions*

A great deal of work has focused on the abundance and function of MDEs due to their importance in agriculture, drug therapy, and translational medicine. DNA microarray studies alone have discovered over 20,000 mRNA targets in bovine MDEs (Izumi et al., 2015) and >100 of these mRNA were found to contain start codons (ATG) (Zempleni et al., 2017). This means that some of these mRNA targets may be translated into proteins and confer cellular functions upon release into recipient cells and tissues. The translation of dietary mRNA to proteins can have major health implications, including the induction of autoimmune responses (i.e., food allergies) in offspring. Furthermore, in terms of early-life programming, transfer of mature mRNA that is ready to be translated into functional proteins may play a large role in the establishment of offspring immunity, which is largely dependent upon maternal milk consumption in early life (Ballard and Morrow, 2013). However, future studies are needed to validate the predicted milk miRNA and mRNA targets and to investigate the exact mechanism of action and transmission across mother-offspring dyads. The biological and nutritional importance of lipids and peptides in MDEs also remains to be explored, although some studies have noted the glycoproteins on the surface of the exosomes may play a role in exosomal uptake (Escrevente et al., 2011). Moreover, future studies are necessary to determine if other maternal factors that are well-documented to influence milk composition, including infections, psychosocial stress, and increased levels of GCs may influence MDE and milk miRNA levels.

Whereas there is consensus on the bioavailability and survivability of MDEs in milk across humans, laboratory and wild mammals, the biological activities and modes of action of its cargo remain a controversial topic. Thus, more research is required to shed light on the mechanistic aspects of MDE transport, the endogenous and exogenous origins, and most importantly, postnatal programming that is associated with changes in MDE cargo. This type of research is especially warranted in natural mammalian systems, where the mechanisms of milk-meditated early-life programming and the corresponding phenotypic and physiological effects experienced in later life remain elusive. This is largely due to the logistical issues surrounding tracking wild animals from birth to adulthood and limited resources that are available for milk collection, storage, and processing at most field locations. Despite these complications, natural populations are better suited for niche-based MDE therapeutics research over the use of laboratory-bred populations. Specifically, the use of MDEs as diagnostic tools to measure maternal health during lactation as well as in environmental/toxicological sciences to trace chemical exposures and detection of viruses and zoonotic pathogen transmission in reproductively active mammals (Escrevente et al., 2011) require the use of natural populations with increased genetic heterogeneity and complex habitats. Moreover, lactating wild mammals are better suited for research that investigates the impact of heat waves, forest/bush fires, and climate change on maternal lactation behavior, breeding, and survival post-parturition. The impact of high ambient temperature on mortality during lactation is well-documented for large-domesticated mammals such as cattle and pigs (Crescio et al., 2010; D'Allaire et al., 1996) as well as laboratory-bred small rodents such as hamsters and Swiss mice (Zhao et al., 2020). Specifically, studies indicate that domesticated lactating large mammals have reduced heat dissipation abilities due to their low surface to volume ratio (Crescio et al., 2010; D'Allaire et al., 1996) and laboratory-bred lactating small rodents are also severely impacted by changes in ambient temperatures due to their high surface to volume ratios (Zhao et al., 2020). However, one must be cautious when expanding these results to wild populations due to the effects of domestication and captivity, where farm and laboratory animals may have lost their natural ability to respond to extreme environmental conditions (Zhao et al., 2020).

Furthermore, it is imperative to account for evolutionary adaptations, predation risk, foraging behavior, habitat loss, and resource scarcity when studying the role of maternal milk in early-life programming in natural systems, because unlike that of laboratory models, a complex set of selective pressures work in unison to modulate lactation biology. Specifically, Srinivasan et al (2018) reported an inextricable link between foraging behavior, predation risk, and lactation metabolomics in dusky dolphins (*Lagenorhynchus obscurus*), where lactating dolphins with calf exhibit heightened risk-averse decision-making strategies such as heightened vigilance and increased hiding time, compared to non-lactating adult dolphins and as a result incurred higher energetic costs and lost foraging calories that affected the milk composition. Likewise, lactating cheetahs with cubs (*Acionynx jubatus*) compensated for the high energy demands of lactation by preferring larger-sized prey, rested less, travelled farther to hunt and seek water (Laurenson, 1995) and lactating black howlers (*Alouatta pigra*) consumed more nutritious fruits and reduced mobility during nursing (Dias et al., 2011). These changes in foraging and predation-risk aversion behavior, and nutrient intake may influence the nutritive and non-nutritive composition of maternal milk and lead to altered developmental outcomes in offspring. Therefore, characterization of developmental outcomes resulting from milk programming should ideally integrate evolutionary adaptations and life-history characteristics specific to each species.

7. Conclusions

Maternal programming is a key determinant of phenotype in mammals. The vast majority of research discussed herein has focused on placental mammals (~6000 species), especially humans and laboratory rodents (Table 1). Its role in monotremes (4 species) and marsupials (~334 species) is essentially unknown, as is its role in the vast majority of wild placental mammals. We have highlighted or alluded to the range of solutions that different mammalian orders, families, and species have with respect to maternal programming. A physiological solution by one species does not necessarily apply to closely related species with an entirely different life history. It must always be borne in mind that these solutions are evolutionary adaptations to ecological problems (abiotic

factors, food limitation, social interactions, predators; MacColl, 2011). Maternal impacts can have lasting fitness consequences on offspring, either through adaptive plasticity in fluctuating environments or by inadvertently programming phenotype-environment mismatch and the developmental origins of disease. Thus, understanding the scope of these effects is of interest to ecologists, evolutionary biologists, and biomedical researchers alike.

We have identified five key maternal cues and areas of research that, in addition to the well-studied influences of diet and stress, are broadening our understanding of maternal effects and the integrative programming of offspring phenotype. Critically, maternal programming cannot be understood by focusing on any single maternal cue in isolation, as many of these routes overlap and interact – both with each other and in their impacts on global offspring phenotype (Table 1). Whereas the interconnected relationships between some of these systems are increasingly being recognized (e.g. the gut-brain axis, Sylvia & Demas 2018), further work is needed to clarify the conditions under which maternal programming effects occur, the relative influence of interacting maternal systems and the nature of their impact on offspring phenotype (neutral, synergistic, or antagonistic effects), as well as their individual and combined contributions to maternal and offspring fitness throughout the lifespan. The outstanding research questions and priorities we have highlighted for maternal androgens, melatonin, microbiome, immunity, and milk should help propel the field of maternal programming effects forward. This will be critical in determining the scope and ubiquity of these effects as adaptive solutions to environmental challenges in the wide diversity of mammalian species.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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