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Adipokines in metabolic and reproductive functions in birds: An overview of current knowns and unknowns

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ABSTRACT

Adipose tissue is now recognized as an active endocrine organ, which synthesizes and secretes numerous peptides factors called adipokines. In mammals, they exert pleiotropic effects affecting energy metabolism but also fertility. In mammals, secretion of adipokines is altered in adipose tissue dysfunctions and may participate to obesity-associated disorders. Thus, adipokines are promising candidates both for novel pharmacological treatment strategies and as diagnostic tools. As compared to mammals, birds exhibit several unique physiological features, which make them an interesting model for comparative studies on endocrine control of metabolism and adiposity and reproductive functions. Some adipokines such as leptin and visfatin may have different roles in avian species as compared to mammals. In addition, some of them found in mammals such as CCL2 (chemokine ligand 2), resistin, omentin and FGF21 (Fibroblast Growth factor 21) have not yet been mapped to the chicken genome model and among its annotated gene models. This brief review aims to summarize data (structure, metabolic and reproductive roles and molecular mechanisms involved) related to main avian adipokines (leptin, adiponectin, visfatin, and chemerin) and we will briefly discuss the adipokines that are still lacking in avian species.

1. Introduction

Like in mammals, the accumulation of excess fat in domestic birds such broilers, has many undesirable consequences such as decreased reproductive performance and reduced feed-conversion efficiencies (Zhang et al., 2018; Zhou et al., 2006). However, a minimum threshold in fat pad above 2.5% has been shown to be necessary for broiler breeder hens to enter lay (van der Klein et al., 2018). White adipose tissue (WAT) is an important energy storage compartment and is the cornerstone of energy metabolism homeostasis (Choe et al., 2016; McGown et al., 2014). In addition to its role in energy storage, WAT also acts as an endocrine tissue by synthesizing and releasing proteins and peptides, referred to as “adipokines.” Avian genomes lack the hallmark gene for brown adipocytes, and this trait makes birds an ideal animal model to study WAT in the absence of brown adipocytes (Abe et al., 2006; Johnston 1971). In mammals, it is well known that deficiency of some adipokines affects not only energy metabolism but also female fertility. Animals with a null mutation in *leptin* (*ob/ob* mice) are obese, hyperphagic and infertile (Chebab, et al. 1996). Peripheral administration of recombinant leptin to *ob/ob* mice completely reverses the obesity by decreasing food intake and increasing energy expenditure and restores fertility (Chebab, et al. 1996). Furthermore, female *adiponectin* null mice

display reduced retrieval of oocytes, disrupted estrous cycle, elevated number of atretic follicles, and impaired late folliculogenesis (Cheng et al., 2016). In chickens, transcriptional analysis of abdominal fat in genetically fat and lean animals has revealed adipokines potentially related to fattening (Resnyk et al., 2013). In females, initial egg production under *ad libitum* feeding is lower in the fat line (Whitehead et al., 1990). Compared with *ad libitum* feeding, food restriction enhances egg production in both lines (Hocking and Whitehead, 1990). The ovaries of fat line females fed *ad libitum* had a high proportion of atretic yellow follicles before ovulation and there is more extensive atresia in small white follicles of fat line birds even when food was severely restricted (Hocking and Whitehead, 1990). Fertility and hatchability are the main indicators of reproductive efficiency in chicken. Zhang et al. (2018) found that these indicators are higher in the lean line than in the fat line (Zhang et al., 2018). The mechanisms underlying the adverse effects of obesity on egg production in chicken requires further clarification. In male, plasma concentrations of FSH, LH and testosterone are higher in the lean males, which may have better promoted their testis development, spermatogenesis and steroidogenesis (Zhang et al., 2018). Similar results have been reported in obese men (Jensen et al., 2004) and mice (Swerdlhoff et al., 1976). Taken together, lean birds (female and male) from divergent genetic selection show better reproductive

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performances. Thus, the genetic selection against abdominal fat deposition positively affects the reproductive performances of birds, possibly by influencing the expression of reproductive hormones and the genes associated with reproduction. However, the molecular mechanisms involved are still unclear. Thus, it is very important to characterize avian WAT and to determine the role of adipokines in the regulation of energy metabolism and reproductive functions in avian species.

The chicken model represents several advantages in studies investigating the adipokines and the link between metabolism and reproduction. Despite decades of intensive genetic selection, the remarkable growth rate of commercial broiler chickens is still improving but is also accompanied by deleterious increases in body fat and skeletal muscle and disorders in metabolism and reproduction (Chen et al., 2006). Furthermore, studies have shown that traits linked to fatness in chickens are similar to those linked to a predisposition for obesity and diabetes in humans (Ji et al., 2012; Jun et al., 2014). A study described the differential expression of adipokines in adipose tissue of two lines of meat-type chickens that have been genetically selected for either high or low visceral abdominal fatness (Resnyk et al., 2013). In addition, overfeeding of hens led to reproductive deficiencies linked to the anarchic follicular hierarchy for females and a delay in sexual maturation in males. Finally, birds are an excellent model to investigate the mechanism and function of hormones since the embryo develops outside the mother's body. *In ovo* injection facilitates the measurement and manipulation of early hormone exposure. These peculiarities make chickens a good animal model to understand the relationship between adipokines, metabolism, and reproduction and their associated mechanisms. However, one of the difficulties to use the avian model is to get good tools (antibodies, ELISA assays.) to study adipokines or other interest molecules. In addition, in contrast to rodents, it is not yet possible to obtain easily transgenic chickens in order to delete specific genes in specific cells to better understand their roles.

In the present review, we will resume some main peculiarities in avian endocrinology (glucose and lipid metabolism and reproduction) and we will describe adipokines that have been identified in birds (leptin, adiponectin, visfatin and chemerin). The involvement of adipokines in the avian embryo development or egg formation will not be discussed here since we recently wrote a review about this aspect (Estienne et al., 2020a). Finally, we will present other adipokines for which the genes have been sequenced but with unclear role until now and also some missing adipokines and their potential consequences in avian endocrinology.

2. Specificities of avian glucose and lipid metabolisms

Chickens exhibit several unique physiological features, which make them an interesting model for comparative studies on endocrine control of metabolism and adiposity. They constitutively exhibit "hyperglycemia" (>200 mg/dL), despite normal levels of a hyperactive endogenous insulin. Large doses of exogenous insulin are required to induce hypoglycemia; furthermore, chickens tolerate doses of exogenous insulin that would be lethal for mammals (Hazelwood and Lorenz 1959; Simon 1989). Thus, chickens are constitutively hyperglycemic and insulin resistant, which mimics the conditions of type 2 diabetes in mammals (Dupont et al., 2009). Enhanced adiposity in chickens is associated with lower fasting plasma glucose, which is variance of hyperglycemia observed in mammals (Leclercq et al., 1987).

In chicken like in human, *de novo* lipogenesis, the conversion of glucose to triglycerides (neutral lipids), takes place primarily in the liver. In chickens, the liver produces >80% of fatty acids from adipose tissue (Griffin et al., 1992) and it is the only organ that responds to feeding/fasting manipulations of insulin signalling (Dupont et al., 1999). Both chicken and mammalian adipocytes develop through a sequence of molecular triggers including activation of CCAAT-enhancer-binding protein alpha (CEBP α) and peroxisome proliferator-activated receptor gamma (PPAR γ) (Wang et al., 2008).

However, a clear point of divergence is their responsiveness to insulin. Unlike in mammals, insulin has minimal effect on glucose uptake in chicken adipose tissue (Tokushima et al., 2005). The avian homolog of the insulin-sensitive glucose transporter GLUT4 has so far not been identified in the current chicken genome database (Coudert et al., 2018) and other avian species of the Bird 10,000 Genomes (B10K) Project while this gene is present in all other non-avian sauropsida species. Insulin stimulates uptake of acetate, which is the preferred substrate for *de novo* lipogenesis in chicken adipocytes, although the magnitude of the effect is relatively modest (Montes et al., 1981). Insulin signalling appears to proceed through tissue specific cascades in chicken metabolic tissues. In liver, insulin elicits a signalling cascade that follows the response in mammals, including tyrosine phosphorylation of insulin receptor β -subunit (IR β), insulin receptor substrate-1 (IRS-1) and Src homology 2 domain-containing substrate (Shc) and activation of phosphatidylinositol 3-kinase (PI3K) (Dupont et al., 1998; Dupont et al., 2008a). The situation in skeletal muscle and adipose tissue is more complex. Tyrosine phosphorylation of IR β and IRS-1 or PI3K activity are not regulated by the insulin status, whereas events downstream of PI3K (e.g. Akt and P70S6K activation) are insulin sensitive (Dupont et al., 2008b, 2012). Insulin does not inhibit adipose lipolysis in chicken; glucagon, rather than catecholamines, is the primary, if not exclusive, lipolytic hormone.

Thus, avian species and more particularly chickens have specificities in glucose and lipid metabolism as compared to mammals. They also present a different regulation in the insulin signalling. Since some of the adipokines either positively or negatively regulate tissue insulin sensitivity in muscle and adipose tissue in mammals, it seems important to better understand the role of these hormones in chickens.

3. Specificities of avian reproductive functions

3.1. Ovary and oviduct

The female reproductive system in the domestic fowl consists of the ovary and the accompanying oviduct. While the female embryo in chicken has two sets of reproductive organs, in adulthood, only one of these, the left, survives and reaches maturity to produce eggs. The single surviving ovary is located in the laying hen just in front of the kidneys in the abdominal cavity and is firmly attached to the wall of the cavity. The ovary is well endowed with blood vessels to ensure there is no hindrance to the transport of nutrients to the developing yolk.

Chicken follicle formation and development are different from mammals. The mature hen ovary contains small pre-hierarchical follicles and maturing preovulatory follicles showing a hierarchy according to their size (F5/6 to F1) (Etches and Pettite 1990). The largest follicle (F1), filled with yolk is first to ovulate, followed by the second-largest follicle (F2) approximately 24–26 h later and this continues down the hierarchy. Similar to mammals, the follicle atresia involving the granulosa cell apoptosis occurs frequently in the prehierarchial follicles (1–8 mm in diameter) (Gilbert et al., 1983). Therefore, all of these characteristics make chicken an ideal model for deciphering the mechanisms regarding ovarian follicular selection and maturation. Each follicle is composed of granulosa cells that are surrounded by theca tissue. The hen granulosa cells from the largest follicles produce large amounts of progesterone but, unlike mammalian species, they don't promote the synthesis of oestrogen (Huang et al., 1979). Indeed, chicken progesterone is synthesized and secreted mainly by granulosa cells whereas theca cells generate oestradiol. Progesterone produced by granulosa cells from mature follicles provides the positive feedback necessary to stimulate a preovulatory surge of LH (Liu et al., 2004). In mammals, this feedback is observed in response to oestradiol. In both mammals and birds, IGF-I has been involved in the regulation of ovarian steroidogenesis. IGF-I stimulates progesterone production from avian granulosa cells (Onagbesan et al., 1999). In birds as in mammals, IGF-1 acts as an autocrine/paracrine regulator of follicular growth and differentiation.

Unlike mammals, the late avian embryo development takes place outside the mother's uterus. Thus, the egg must contain all the nutrients to allow for embryo development. The oviduct will allow for the formation of the egg but also its fertilization (Estienne et al., 2020a).

3.2. Testis

The male reproductive organs in the domestic fowl consist of two testes, each with a deferent duct that leads from the testes to the cloaca. Fowls do not have a penis such as is found in other animals. The testes are bean-shaped bodies located against the backbone at the front of the kidney and at the opposite of mammals are functionally active at 41 °C, the body temperature. Their size is not constant and they become larger when the birds are actively mating. The left testis is often larger than the right. As the site of spermatogenesis and testosterone production, the testis plays a central role in the male reproductive system in chickens as in mammals. In the male chicken, as with other birds, the testes produce sperm, and then the sperm travels through a vas deferens to the cloaca. Avian sperm remains viable at body temperature. Consequently, the avian male reproductive tract is entirely inside the body. In this way, the reproductive system of male birds differs from that of male mammals. The reproductive tract in male mammals is outside the body because mammalian sperm does not remain viable at body temperature. The testis is a unique organ in the male reproductive system, and it is responsible for spermatogenesis and testosterone production. At the opposite of mammals, chicken testis presents some particularities such as temperature of 41–43 °C because of the location of testes in the deep body and absence of the pampiniform structure (Lake, 1971). Spermatozoa are produced in a shorter period compared with other vertebrates since the duration of the spermatogenic process is 14 days in chickens, 35 days in mice, and 64 days in humans (Adler, 1996), and the testicular activity is strongly controlled by the photoperiod, suggesting a relative plasticity and rapidity to produce sperm across seasons (De Reviere et al., 1980). In addition, in chickens the testicular growth starts slowly until 5 weeks of age (1 mg/day) and then progresses very quickly between 6 and 20 weeks (87 mg/day; Reviere, 1971). In both mammals and birds, several studies have associated the testis size and the production and quality of germ cells with the number and function of Sertoli cells (De Reviere et al., 1980). On the basis of morphological analysis, Sertoli cells of the domestic fowls present high similarities with Sertoli cells in mammals (Kodani and Kodani, 1966). Cells produced numerous projections and the cytoplasm contained numerous lipid droplets associated with high cholesterol levels. Sertoli cells are able to synthesize cholesterol (Maboundou et al., 1995). In addition, isolation of immature chicken Sertoli cells expressed AMH protein, known to be produced in immature Sertoli cells in others species (Tran et al., 1987). Even if most avian Sertoli cell features are similar to those of others mammals, purified chicken Sertoli cells expressed an active 3 β -HSD in contrast to rodent Sertoli cells (Woods and LV, 1966). This enzyme is involved in steroidogenesis (Purohit et al., 1977), it induces the conversion of cholesterol to pregnenolone or pregnenolone to progesterone.

4. The main avian known adipokines

In avian species, the role of leptin was under debate until the gene sequencing. Recently, three novel adipokines have been discovered: adiponectin (ADIPOQ, ACRP30), visfatin (NAMPT, PBEF), and chemerin (RARRES2, TIG2). However, their mode of action between mammalian and avian species is different due to the different reproductive and metabolic systems.

4.1. Leptin

While the leptin and leptin receptor are being intensively studied in mammals, and evidence for the therapeutic value in humans continues to accumulate (Friedman and Halaas 1998), it remains unclear whether

the associated control mechanism is conserved in non-mammalian vertebrates such as the avian species.

4.1.1. Structure

In mammals, leptin is a multifunctional nonglycosylated hormone, with a molecular weight of 16 kDa, mainly synthesized and secreted in proportion to body mass by preadipocytes and adipocytes. Its precursor includes 167 amino acid residues on the front and 21 amino-acid signal peptides on the back (Friedman and Halaas 1998). Leptin circulates in blood relatively at 1–10 ng/ml concentrations (Fig. 1).

In avian species, the identification of leptin has been hampered for decades, despite intensive efforts to find the gene sequence. The first avian leptin transcripts were discovered only a few years ago in the Peregrine falcon (Prokop et al., 2014), the Japanese quail (Wang et al., 2016), the Zebra finch (Huang et al., 2014) and the Rock dove (Friedman-Einat et al., 2014) in a GC-rich locus presenting some difficulties to sequence. The full open reading frames in the leptin transcripts were identified a bit later in chicken and duck with only 26–30% identity with human leptin protein (Seroussi et al., 2016) but the chromosomal location and the sequence of chicken locus containing the leptin gene were only resolved recently (Seroussi et al., 2017; Beauclair et al., 2019).

Until recently, chicken leptin polypeptide was undetectable in blood and raised the question about its presence in peripheral circulation (Seroussi et al., 2016). Its expression was reported in non-adipose tissues, mainly in brain and pituitary (Seroussi et al., 2016; Seroussi et al., 2017) such as cerebellum, hypothalamus and cerebrum tissues of red junglefowl or for the first time expression along the digestive system (duodenum, caecal tonsil, ileum, and pancreas) in chicken (Seroussi et al., 2019).

4.1.2. Receptor and cell signalling

In mammals, leptin exerts its biological functions through leptin receptor (LEP-R). After leptin is bound to the LEP-R, it activates multiple signalling pathways such as Janus kinase 2-signal transducer and activator of transcription 3 (JAK2-STAT3), mitogen-activated protein kinases (MAPKs) and phosphatidylinositol 3 kinase/serine-threonine kinase (PI3K/AKT).

In chicken, the leptin receptor gene, has been cloned and sequenced (Horev et al., 2000). Chicken LEP-R shares functional motifs and consensus sequences with their mammalian orthologs. These include their corresponding ligand-binding domains, and other consensus sequences implicated in their respective signal transduction pathways (Horev et al., 2000). Ohkubo and Adachi et al. (2008) found that chicken LEP-R protein occurred in chicken brain and hepatocellular carcinoma cell line (LMH) cells, a chicken hepatoma cell line (Adachi et al., 2008). Adachi et al. (2008) found that by combining with murine leptin, chicken LEP-R could activate JAK-STAT pathways, in CHO-K1 cells, a Chinese hamster ovary cell line. Despite this experiment, the molecular mechanism of LEP-R-mediated signal transduction pathways is unclear in adipocytes (Adachi et al., 2008). The availability of a functional chicken leptin receptor prompts studies targeting leptin receptor, which substantially augmented leptin bioactivities in both chicken hens and pullets (Lei et al., 2015).

4.1.3. Physiological actions

4.1.3.1. Glucose and lipid metabolism. In non-avian organisms, leptin, which circulates in the blood with a circadian rhythmicity, acts on the brain to regulate appetite and feeding behavior, metabolism and energy homeostasis, and satiation responses during feeding (Penicaud et al., 2012). In mammals, a positive correlation exists between the amount of circulating leptin and the extent of body fat in mammals (Banks et al., 1996). With respect to the immune response, various studies have shown that leptin modulates innate and adaptive immunity (Monteiro et al.,



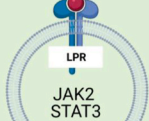






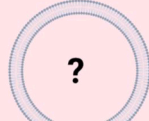

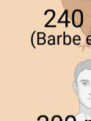

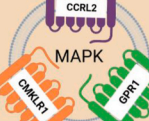
ADIPOKINE	BLOOD CONCENTRATION	MAIN TARGET CELLS	RECEPTOR
Leptin 	 1-10 ng/ml (Licinio et al 1998)	Reproductive and stress axis (Seroussi et al 2016) Brain (Penicaud et al 2012)	 LPR JAK2 STAT3 (Münzberg and Morrison 2015)
Adiponectin 	 3 µg/ml (Barbe et al 2020) 10 µg/ml (Hotta et al 2000)	Gonadal cells and peripheral tissues (Chabrolle et al 2007a) Reproductive and peripheral tissues (Yamauchi et al 2014)	 AdipoR1 AdipoR2 APPLs MAPK ERK1/2 P38 AMPK PPARalpha (Gan et al 2015)
Visfatin 	 160 ng/ml (Barbe et al 2020) 7-21 ng/ml (Karatas et al 2015)	 Muscles (Krzysik-Walker et al 2008) Ubiquitous (Estienne et al 2020)	 ?
Chemerin 	 240 ng/ml (Barbe et al 2020) 200 ng/ml (Marti et al 2021)	 Ubiquitous (Estienne et al 2020) Ubiquitous (Estienne et al 2020)	 CCRL2 MAPK ChemK1 GPR1 (Kennedy and Davenport 2018)

Fig. 1. Plasma concentration, target cells and receptors of leptin, adiponectin, visfatin and chemerin in chicken and human.

2019). In mice, mutations of leptin or leptin receptor causes to an obesity and diabetes.

In chicken, Ban et al. (2017) showed that knockdown of LEP-R influences mRNA expression of genes associated with signal transduction, including JAK2, STAT3, SOCS3, as well as genes related to fatty acid metabolism, like CPT1 (Carnitine palmitoyltransferase 1) (Ban et al., 2017). These results suggested that LEP-R plays a certain role in regulating genes in the complicated gene network of preadipocytes. However, the role of leptin in avian species is still unclear and chicken leptin could not be an important adipokine involved in the regulation of energy metabolism.

4.1.3.2. Reproductive (gonadal) functions. In mammals, knock out leptin mice are infertile. They are unable to produce GnRH (gonadotropin-releasing hormone) from the hypothalamus. Consequently, the release of LH (luteinizing hormone) and FSH (follicle stimulating hormone) from the pituitary are negatively impacted (Tsatsanis et al., 2015). But these negative effects on the reproductive functions are restored with exogenous administration of leptin (Kawwass et al., 2015). In birds, leptin receptors have a high level of expression in the hypothalamic-pituitary and adrenal axes suggesting that leptin is more involved in the regulation of reproduction and stress response rather than metabolism (Seroussi et al., 2016). In chicken as in mammals leptin and leptin receptor are also expressed in gonads (Seroussi et al., 2016).

4.1.3.2.1. Ovary. In mammals, some evidence indicates that leptin can directly affect ovarian functions (Estienne et al., 2020a). Indeed, leptin antagonizes *in vitro* insulin-like growth factor-I-induced steroidogenesis in granulosa and theca cells of mammalian ovaries. At the opposite, it enhances *in vitro* oocytes nuclear and cytoplasmic

maturation in various species and *in vitro* embryo development in pigs (Estienne et al., 2020a).

In chicken, Cassy et al. suggested positive effects of leptin on follicular maturation (Cassy et al., 2004). In hens, the *in vivo* injection of the mammalian leptin isoform improves the negative effects of fasting on ovarian function by attenuating follicular apoptosis, delaying the cessation of egg laying and influencing ovarian steroidogenesis (Paczoska-Eliasiewicz et al., 2003). Thus, leptin could exert beneficial effect on oocyte maturation in both birds and mammals.

4.1.3.2.2. Testis. In mammals, leptin and its receptor have a different localization on the male tract depending on the species. In human expression of leptin is in seminiferous tubules, Leydig cells and seminal plasma. Moreover, human seminal plasma and sperm contain leptin receptor (Aquila et al., 2005). In rats, leptin receptor is expressed in Leydig and Sertoli cells and germ cells (Tena-Sempere et al., 2001) whereas in dogs its receptor was missing in Leydig and Sertoli cells but expressed in spermatocytes and spermatids (Muller et al., 2017). This adipokine presents an effect on the spermatozoa functionality such as motility. Indeed, several studies in human showed an association with a higher concentration of leptin in seminal fluid and spermatid disorders (Ni et al., 2015). Hang et al. showed that a higher concentration of leptin could lead to an increase in the markers of oxidative stress and apoptosis on sperm (Wang et al., 2015). Also, Caprio et al. demonstrated in adult rats that leptin inhibited *in vitro* production of testosterone in response to hCG in Leydig cells (Caprio et al., 2003). All these data suggest a role of leptin in sperm parameters with a potential impact on male fertility and may contribute in reproduction and metabolism functions in case of disorders.

In chicken, leptin and LEP-R are expressed at the mRNA level in the

testis (Seroussi et al., 2016) but the protein location is unknown due to the absence of specific antibodies tools and functions in birds are unclear.

Taken together, unlike in mammals, leptin is not mainly expressed in adipose tissue but it is expressed in hypothalamus, pituitary and digestive system in birds. Since LEP-R is present in more than 80% of all tissues in which leptin is found, it is hypothesized that leptin acts predominantly in an autocrine or paracrine but not in an endocrine manner as described in mammals. These data suggest also that leptin may not play a crucial role in avian appetite control but could be involved in the digestive functions. Concerning the reproductive functions, unfortunately, no information on a potential role of leptin on the reproductive axis is available in chickens. Therefore, further investigations are required to determine the role of leptin in the metabolism and reproductive functions.

4.2. Adiponectin

4.2.1. Structure

In mammals, adiponectin also termed Acrp30 (adipocyte complement-related protein), apMI (adipose most abundant gene transcript I), GBP28 (gelatin binding protein 28), or AdipoQ, is the most abundant protein in human adipose tissue, and the most abundant hormone in human plasma (Arita et al., 1999). It exerts critical metabolic functions (Kadowaki and Yamauchi 2005). After secretion of adiponectin, it is transported into circulation system under the form of different sizes of molecular weights including trimer, hexamer and high molecular weight form (Kadowaki and Yamauchi 2005).

In chicken, adiponectin gene encodes a polypeptide of 240 amino acids (30 kDa) (Yuan et al., 2006). The chicken cDNA (735 nucleotides) is 65–68% homologous to various mammalian adiponectin cDNA and their proteins are highly conserved (Maddineni et al., 2005; Yuan et al., 2006). In chicken, plasma and adipose tissue adiponectin is predominantly composed of a unique multimeric heavy molecular weight (HMW) isoform (Hendricks, et al. 2009), in contrast to mammalian adiponectin which is found three distinct oligomers as low (LMW), medium (MMW) and heavy molecular weight (HMW) (Ramachandran et al., 2013). A mass spectrometric analysis revealed that chicken adiponectin contains a greater number of lysine residues in the collagenous domain compared to human adiponectin, potentially responsible for multimerization and formation of a stable unique HMW adiponectin isoform (Hendricks, et al. 2009). In chicken, adiponectin gene is also expressed in the liver, diencephalon, anterior pituitary gland, kidney, ovary, spleen and skeletal muscle besides adipose tissue (Maddineni et al., 2005). In chicken like in mammals, adiponectin circulates in blood relatively at high concentrations ($\mu\text{g/ml}$) (Fig. 1).

4.2.2. Receptor and cell signalling

In mammals, different forms of adiponectin exert their biological functions by binding to two main specific seven transmembrane domains receptors named AdipoR1 and AdipoR2 on target cells (Yamauchi et al., 2014). These two receptors can bind to two APPLs (adaptor proteins containing the pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif) APPL1 and APPL2 (Liu et al., 2017). Adiponectin receptors are ubiquitously expressed in various tissues, where most abundant expression of AdipoR1 was in muscle tissues and AdipoR2 presents a predominant expression in liver tissues (Kadowaki and Yamauchi 2005). The general physiological function of adiponectin is to enhance fatty acid oxidation and glucose utilization and improve insulin sensitivity (Kadowaki and Yamauchi 2005).

In chicken, adiponectin receptors. AdipoR1 and AdipoR2 have 91% and 82% amino acid identity, respectively with the mammalian forms. The important homology between avian and mammalian adiponectin receptors may suggest that both genes are evolutionarily conserved (Ramachandran et al., 2013). We find also in turkey and goose similar expressions of adiponectin and adiponectin receptors (Cao et al., 2015;

Diot et al., 2015b). Zhang et al. showed that in Tibetan chicken, adiponectin system is gender and age dependent on adipose tissue and skeletal muscle (Zhang et al., 2017). Maddineni et al. described expression of adiponectin and AdipoR2 are higher in females than males while AdipoR1 is higher in males (Maddineni et al., 2005). In chicken like in mammals, binding of adiponectin activates different signalling pathways such as AMPK, MAPK activated p38, ERK1/2 and PPAR alpha, involved in metabolic processes like the release of insulin, inhibition of lipid synthesis, glucose uptake and reproductive processes (Chabrolle et al., 2007a; Gan et al., 2015, Jun et al., 2014; Fig. 1).

4.2.3. Physiological actions

4.2.3.1. Glucose and lipid metabolism. In mammals, adiponectin is mainly expressed by adipose tissue and released into the bloodstream. Circulating levels of adiponectin are negatively correlated with the degree of adiposity and are reduced in case of obesity, insulin resistance and type 2 diabetes (Yamauchi et al., 2003). Thus, adiponectin exerts effects directly on hepatocytes, pancreatic cells and adipocytes to promote glucose and lipid homeostasis. It improved lipid oxidation, insulin sensitivity and decreased steatosis, fibrosis and apoptosis (Yamauchi et al., 2014). In mice, Hu et al. showed a significant down regulation of adiponectin mRNA observed in adipose tissues from obese mice and human (Hu et al., 1996). In addition, an administration of adiponectin increased insulin sensitivity.

In chicken, Maddineni et al. showed that fasting can influence the expression of adiponectin with a decrease of its levels in adipose tissue, liver and pituitary gland (Maddineni et al., 2005). Adiponectin plays a critical role as a negative regulator in fat deposition in chickens (Yan et al., 2014). In contrast to a report in mice where HFD (High Fat Diet) feeding decreased total adiponectin plasma levels and adiponectin mRNA expression in adipose tissues (Liu et al., 2013), chickens with HFD feeding showed an increase in the mRNA expression of adiponectin and its receptors in fats and, especially, circulating levels of macromolecular adiponectin (Chen et al., 2018). However, plasma total adiponectin is negatively correlated to plasma glucose in turkeys hens (Diot, et al. 2015a,b). In humans, plasma adiponectin levels are negatively correlated with adiposity, insulin resistance, type 2 diabetes, and metabolic syndrome (Lihn et al., 2005). These results suggest that avian adipose tissue expresses adiponectin and its receptors and could be involved in the regulation of insulin sensitivity like in mammals.

4.2.3.2. Reproductive (gonadal) functions. In several mammals, a sexual dimorphism has been already described concerning plasma adiponectin. Indeed, males have lower plasma adiponectin levels than females (Rak et al., 2017). Concerning the reproductive functions, adiponectin and its receptor are expressed in hypothalamo-pituitary gonadal axis in many mammalian species (Rak et al., 2017). Moreover, adiponectin has been shown to regulate *in vitro* and *in vivo* kisspeptin gene expression and gonadotropin secretion and consequently expression of GnRH (Cheng et al., 2016; Rak et al., 2017).

4.2.3.2.1. Ovary. In most of the mammalian species, adiponectin has been also demonstrated to regulate ovarian steroidogenesis (Rak et al., 2017). Adiponectin is expressed in oocytes and is almost absent cumulus cells and granulosa while AdipoR1 and AdipoR2 are present in granulosa cells in rodents and humans (Chabrolle et al., 2007b; Chabrolle et al., 2009). Moreover, in mice, adiponectin supplementation during maturation *in vitro* had positive effects on meiotic progression and initial embryo development (Richards et al., 2012).

In chicken, adiponectin gene was mainly found more in theca cells than granulosa cells from F4–F1 preovulatory follicles in the hen (Chabrolle et al., 2007a). Theca layer cells dispersed from preovulatory and prehierarchal follicles were found to synthesize and secrete a 720 kDa HMW isoform of adiponectin *in vitro* (Hadley et al., 2020). Concerning its receptors, AdipoR1 levels expression is lower in theca cells

than granulosa cells while levels of AdipoR2 were unchanged in both ovarian chicken cells. Overall suggested an effect on the development of chicken preovulatory follicle and oocyte maturation (Chabrolle et al., 2007a; Ramachandran et al., 2013). Adiponectin has also been reported to enhance IGF-1-induced progesterone secretion in hen preovulatory follicle granulosa cells (Chabrolle et al., 2007a). Adiponectin and receptors are expressed in embryos at different stages of development in chickens (Mellouk et al., 2018a).

4.2.3.2.2. Testis. Adiponectin and its receptors are also expressed in the male reproductive tract. They are present in human testes (seminiferous tubules and interstitial tissue), epididymis, Leydig cells and spermatozoa (Elfassy et al., 2018). In mice, loss of AdipoR2 induced seminiferous tubular atrophy associated with aspermia and reduction of testes weight (Elfassy et al., 2018). Choubey et al. used a treatment of exogenous adiponectin in aged mice and they showed improvements in testicular mass, insulin receptor expression and testosterone synthesis in the testis and a reduction in the oxidative stress. Thus, adiponectin treatment can improve testicular functions of senescent animals (Choubey et al., 2019).

In chicken males, adiponectin, AdipoR1 and AdipoR2 are also expressed in chicken testes. More precisely, adiponectin and AdipoR1 were localized to the peritubular and Leydig cells and AdipoR2 was mainly observed in Sertoli cells, spermatids and spermatozoa suggesting adiponectin can affect maturation and differentiation of spermatocytes (Ramachandran et al., 2013). Plasma adiponectin levels are higher in sexually mature than in immature animals and this is associated with a significant increase in adiponectin receptors' expression in mature chickens. It could be a result of the higher activity related to spermatogenesis testicular hormone production (Ocon-Grove et al., 2008).

Taken together, chicken adiponectin is mainly found as multimeric HMW isoforms in plasma, and tissues. Concerning the metabolic aspect, since plasma adiponectin is negatively correlated to plasma glucose in turkey hens, we can speculate that adiponectin could play a potential role in the regulation of insulin sensitivity in avian species. Concerning the reproductive aspects, adiponectin is expressed exclusively in the theca cells of ovarian follicles in broiler breeders and laying hens suggesting an autocrine/paracrine effect on the steroidogenesis. In addition, since we showed that adiponectin is able to increase IGF-1-induced progesterone, we can suggest that adiponectin could be an actor involved in the metabolic status on follicular development and the age at the first egg. In male, adiponectin and its receptors could exert beneficial effects on chicken male reproductive functions including sexual maturity.

4.3. Visfatin

Another potentially important adipokine, visfatin (also named Nampt), has been implicated in the energy metabolism regulation in mammals and birds. In mammals, two isoforms of Nampt have been described. Intracellular Nampt (iNampt), which plays a central role in maintaining the activity of NAD-dependent enzymes, is implicated in the regulation of cellular metabolism in response to nutrient availability, maturation and cell survival (Garten et al., 2015). On the contrary, the other isoform, extracellular Nampt (eNampt), is secreted by different cell types and play the role as an adipokine (a real mediator of inter-organ crosstalk) in mammals (Carbone et al., 2017).

4.3.1. Structure

In 1994, visfatin gene has been isolated in humans as a pre-B cell colony-enhancing factor (PBEF) from human peripheral blood lymphocyte capable of initiating the maturation of the precursors of B cells. Visfatin gene was found on the long arm of chromosome 7 and codes for a 52 kDa secreted protein for review (Carbone et al., 2017; Garten et al., 2015).

In chicken, visfatin gene has been cloned from adult liver and gonads. It encoded a protein of 493 amino acids and it shared a high

protein sequence identity with both human and rat visfatin (94%, Li, et al., 2012). Visfatin mRNA has been located in the brain, heart, intestine, kidney, liver, lungs, muscles and also in adipose tissue (Li et al., 2012). It is sex and tissue dependent on chicken (Ons et al., 2010). In contrast to mammals, avian visfatin is higher expressed in skeletal muscle than in visceral fat (Krzysik-Walker et al., 2011; Krzysik-Walker et al., 2008). Increased visceral adiposity and hyperglycemia are correlated with elevated plasma visfatin levels in humans. However, fasting and refeeding don't affect plasma visfatin levels in the chicken (Mellouk et al., 2018b). Moreover, visfatin circulates in blood relatively at about 160 ng/ml concentrations that is significantly higher than humans (Fig. 1).

4.3.2. Receptor and cell signalling

In mammals, action of visfatin has been controversial because its receptor(s) is still unknown (Fig. 1) but this hormone was characterized as an analogue of the insulin with an active binding site on the insulin receptor. Consequently, signalling pathways of visfatin remains unclear.

4.3.3. Physiological actions

4.3.3.1. Glucose and lipid metabolism. Visfatin has been identified as a cytokine hormone involved in metabolic (obesity, type II diabetes) and immune disorders. In human, increased circulating visfatin levels have been associated with obesity (Carbone et al., 2017).

In chicken, visfatin expression is higher in skeletal muscle than visceral adipose tissue suggesting that visfatin is a potential myokine. Its expression is further elevated with age of chicken. Also, visfatin can decrease the expression of MYF5 (Myogenic factor 5), a marker of skeletal muscle development (Krzysik-Walker et al., 2008). Furthermore, Cline et al. showed that in chicken, visfatin causes orexigenic effects and increases the feed intake (Cline et al., 2008).

4.3.3.2. Reproductive (gonadal) functions. Concerning reproductive functions, in mammals, visfatin can act in female (granulosa and theca cells in the ovary) and male (sertoli and Leydig cells and spermatozoa) gonads.

4.3.3.2.1. Ovary. Concerning women subjected to *in vitro* fertilization (IVF) procedures, visfatin concentrations in follicular fluid can be a predictive indicator for ovarian reserve and number of oocytes retrieved. However, in this study there was no correlation with the plasma visfatin concentration suggesting an independent visfatin regulation at the ovarian level (Shen et al., 2010). Moreover, visfatin is expressed in human and bovine granulosa cells and increases secretion of oestradiol and progesterone induced by IGF-1 (Reverchon et al., 2013; Reverchon et al., 2016). Choi et al. also showed that visfatin administration improves the developmental competency of oocytes and fertility of aged female mice (Choi et al., 2012).

Contrary to mammals, in turkeys, visfatin is expressed mainly in theca cells and in a less important manner in granulosa cells, with a higher plasma level at the end of lay periode (Diot et al., 2015b). Moreover, in contrast to mammals, visfatin reduces IGF-1-induced progesterone secretion in chicken granulosa cells (Diot et al., 2015a).

4.3.3.2.2. Testis. Visfatin is present in human testes and spermatozoa with a higher expression in immature spermatozoa (Riammer et al., 2016). It is also expressed in rat testes but its levels decreased after a D-galactose treatment inducing aging. Its expression also decreases in Leydig cells leading to decreased serum testosterone levels suggesting a role of visfatin in aging testis regulating spermatogenesis and steroidogenesis (Jeremy et al., 2017). In chickens, visfatin plasma levels are higher in adult than in prepubertal males (Ocon-Grove et al., 2010).

Overall, visfatin is mainly a myokine in chicken. All the data also suggest that visfatin is present and it is involved in the gametogenesis in avian species as in mammals. In hen, visfatin is expressed in granulosa and theca cells from hierarchical follicles. Since visfatin decreases in

vitro IGF-1-induced progesterone secretion, we can speculate that visfatin may play a role in ovulation in hens. Indeed, unlike in mammals, progesterone triggers ovulation in birds, which causes a surge in LH production (Sauveur and de Reviere, 1988). One hypothesis is that a decrease in visfatin plasma levels before the increase in progesterone secretion is responsible for the pre-ovulatory LH surge; however, cyclical changes in the plasma levels of visfatin in hens have yet to be determined.

4.4. Chemerin

4.4.1. Structure

In mammals, Chemerin also called TIG2 (tazarotene-induced gene 2) or RARRES2 (retinoic acid receptor responder 2) is a factor secreted predominantly by adipose tissue and liver and expressed in several tissues like pancreas, placenta, skin, kidneys, intestines and gonads (Helfer and Wu 2018). After truncation of the 20 amino acids signal peptide, pre-prochemerin is released into the extracellular compartment as an inactive prochemerin of 143 amino acid. Then prochemerin requires a second cleavage of the C-terminal to generate an active form of chemerin (Helfer and Wu 2018). In different tissues, various isoforms of chemerin have been identified depending on proteases for cleavage (Helfer and Wu 2018).

In chicken, chemerin and its receptors Chemokine like receptor 1 (CMKLR1), and G protein-coupled receptor 1 (GPR1) have low amino acid identities of 36%, 56%, and 64% with human chemerin and its receptor, respectively (Estienne et al., 2020a). In birds, plasma chemerin was determined by using specific ELISA. However, the measured isoform in these assays is not indicated. In chicken, plasma chemerin concentration is similar to human (Fig. 1). In the literature, the blood concentration of total chemerin was reported to be about 200 ng/ml in humans (Fig. 1).

4.4.2. Receptor and cell signalling

In mammals, chemerin is able to bind three receptors coupled to G proteins: CMKLR1 also known as chemR23, GPR1 and C-C motif chemokine receptor like 2 (CCRL2). CMKLR1 and GPR1 are coupled to the Gi/o family of G protein and inhibit the cAMP signalling pathway but promote the PLC, PI3K and MAPK pathways, calcium mobilization and the recruitment of beta-arrestin which activates ERK1/2 signalling pathway (Kennedy and Davenport 2018). Moreover, the binding of chemerin to CMKLR1 and GPR1 promotes the internalization of these receptors while CCLR2 does not induce an intracellular signalling known to date. The current hypothesis is that CCLR2 would be a receptor able to increase the local concentration of chemerin for CMKLR1 receptor. CCRL2 exhibits low sequence homology with CMKLR1 and GPR1 (De Henau et al., 2016). So, each chemerin receptor displays selective signalling pathways (Fig. 1).

4.4.3. Physiological actions

4.4.3.1. Glucose and lipid metabolism. Chemerin was described as a regulator of several physiological processes like adipogenesis, blood pressure, immune system, angiogenesis and inflammation in skin and adipose tissue (Mattern et al., 2014). It is also associated with metabolic disorders including food intake and insulin sensitivity. Goralsky et al. showed the invalidation of chemerin or CMKLR1 genes lead to a decrease the expression of genes involved in glucose and lipid metabolism like *GLUT4* in mice (Goralski et al., 2007). In mice, CMKLR1 deficiency leads to a glucose intolerance, promotes insulin resistance and decreases adiposity but a injection *in vivo* of recombinant chemerin exacerbates glucose intolerance in obese/diabetic mice (Ernst et al., 2012). In humans, plasma chemerin levels are positively correlated with body fat, plasma glucose and triglyceride levels and lipid metabolism (Bozaoglu et al., 2007).

In contrast to mammals, plasma chemerin is associated with leanness and not with fattening in turkeys (Diot et al., 2015b) and chicken (Mellouk et al., 2018b). In addition, intraperitoneal chicken chemerin injection decreases food intake in broiler (Estienne et al., 2021). Also, in our laboratory, we showed that plasma chemerin was positively associated with the index of oxidative stress in response to a dietary grape seed extract supplementation in hens (Barbe et al., 2020). Thus, plasma chemerin could participate in the oxidative stress regulation of avian species.

4.4.3.2. Reproductive (gonadal) functions

4.4.3.2.1. Ovary. Several studies showed the expression of the chemerin system in ovarian cells including granulosa and theca cells, corpus luteum and oocytes in different mammalian species including human (Reverchon et al., 2014; Reverchon et al., 2012). In human granulosa cells, chemerin reduces steroidogenesis and cell proliferation induced by IGF-1 (Reverchon et al., 2012). Similar data were obtained in mice. In addition, in mice corpus luteum, chemerin/GPR1 signalling directly or indirectly regulates progesterone synthesis and secretion during the processes of corpus luteum formation, and PGF2 α -induced luteolysis (Yang et al., 2016). In bovine species, chemerin through CMKLR1 also exerts inhibitory effects on progesterone and oestradiol secretion, StAR and P450arom and cholesterol synthesis in granulosa cells and it also induces a blockage of *in vitro* oocyte maturation at germinal vesicle stage (Reverchon et al., 2014). Moreover, chemerin could be involved in reproduction disorders like Polycystic Ovary Syndrome (PCOS) (Bongrani et al., 2019; Estienne et al., 2019). Moreover, CMKLR1 gene deletion attenuates the effects of chronic DHT (5 α -dihydrotestosterone) treatment on ovarian function in experimental PCOS model in rat (Tang et al., 2016). Thus, CMKLR1 gene deletion protects against the damage caused by chronic DHT treatment on ovarian function in rodents suggesting that androgen-induced PCOS might be prevented through therapeutic targeting of CMKLR1. In avian species, chemerin and its receptor have been shown to be present in the ovary. Mellouk et al. showed chicken with food restriction have higher chemerin levels than *ad libitum* hens associated to a better egg quality and fertility (Mellouk et al., 2018a; Mellouk et al., 2018b). Then, contrary to mammals, chemerin and its receptors are more expressed in theca cells than in granulosa cells in turkeys. In this latter species, plasma chemerin levels decrease at the end of laying period and they are negatively correlated with plasma cholesterol, triglycerides and phospholids (Diot et al., 2015b). The chemerin system are also present in the chicken embryo but its role in the embryo development is still unknown (Mellouk et al., 2018a).

4.4.3.2.2. Testis. Concerning the male, chemerin and its three receptors are present in the testis and chemerin, CMKLR1 and GPR1 have been localized in Leydig cells and little in germ cells in human and rats (Li et al., 2014). Chemerin appears as a negative regulator of male steroidogenesis since it inhibits testosterone production from Leydig cells in response to hCG (Li et al., 2014). Chemerin could also have a negative impact on maturation and motility of spermatozoa (Elfassy et al., 2018).

Like mammals, chemerin and its main receptor CMKLR1 are present in chicken testes with the lowest expression for adult chicken compared to immature animals (Estienne et al., 2020b). Estienne et al. have shown that *in vitro* recombinant chicken chemerin reduced motility of spermatozoa and inhibits testosterone production by the testes (Estienne et al., 2020b). They demonstrated that chemerin seminal plasma concentration but not chemerin blood plasma was negatively correlated with spermatozoa concentration and motility *in vivo* in chicken sperm. Furthermore, chicken sperm treated by chemerin reduced egg fertility during the four first days after artificial insemination.

Taken together, chemerin and chemerin receptors are expressed in chicken peripheral and gonadal tissues. Unlike mammals, plasma chemerin is negatively correlated to fattening whereas it decreases food intake. Concerning the reproductive functions, all the results in male

suggest that chemerin is a negative regulator for the gonadal functions. These data could be interesting for genetic selection to eliminate bad roosters.

5. Others adipokines found in the avian genome but not yet studied

As shown in Table 1, others adipokines gene including *apelin*, *adipolin*, *Neuregulin-4*, *NOV/CCN3*, ...that have been described in chicken but their role is mostly unknown.

One example is the Tumor Necrosis Factor alpha (TNF- α) gene. TNF-

Table 1

List of the some adipokines and their functions knowns in mammals (human or mice) and avian (chicken) species.

Adipokine	Gene, accession number (human). Location on chromosome (chr)	Gene, accession number (chicken). Location on chromosome (chr)	% identity (protein) and homology (gene)	Main functions (human)	Main functions (chicken)
Leptin	NM_000230. Chr 7	LN794245. Chr 1	24 and 41%	Decreases food intake, regulation of metabolism (Tsatanis, 2015) and reproduction (Estienne et al., 2020a)	Could regulate stress response and reproduction (Seroussi et al., 2016)
Adiponectin	EU420013. Chr 3	AY523637. Chr 9	67 and 67%	Regulation of lipid oxidation, insulin sensitivity, glucose homeostasis and reduce apoptosis (Yamauchi et al., 2014) and reproduction (Rak et al., 2017)	Negative role in fat deposition (Yan et al., 2014) and regulation of reproductive functions (Chabrolle et al., 2007a)
Resistin (FIZZ3)	AF323081. Chr 19	missing		Pro-inflammatory, glucose metabolism, resistance to insulin (Zhao et al., 2019). Reproduction (Estienne et al., 2019)	
Visfatin (PEBF)	NM_005746. Chr 7	AY946242. Chr 1	94 and 84%	Improves insulin secretion, increases feed intake, predictor for ovarian reserve (Shen et al., 2010) and increases steroidogenesis (Reverchon et al., 2016)	Potential myokine (Krzysik-Walker et al., 2008). Regulates feed intake (Cline et al., 2008) and regulates <i>in vitro</i> ovarian functions (Diot et al., 2015a)
Chemerin (RARRES2)	NM_002889 XM_005250032. Chr 7	KY346986. Chr 2	38 and 58%	Adipogenesis, blood pressure, immune system and fat metabolism (Mattern et al., 2014). Regulates reproduction function (Reverchon et al., 2014)	Reduces food intake (Estienne et al., 2021) and oxidative stress (Barbe et al., 2020). Regulates reproduction function (Mellouk et al., 2018a)
Apelin	BC021104 Chr X	Predicted. XM_015278386. Chr 4	36 and 48%	Angiogenesis and ovarian steroidogenesis (Estienne et al., 2019)	Potent angiogenic factor (Cox et al., 2006)
Adipolin (FAM132A; C1QTNF12)	NM_001014980 XM_928940 XM_938281. Chr 1	Predicted. XM_417583. Chr 21	54 and 61%	Insulin sensitivity, glucose tolerance and anti-inflammatory (Knights et al., 2014)	Unclear, regulation by feed deprivation (Bornelöv et al., 2018)
CCL2 (MCP-1)	NM_002982 Chr 17	unknown	unknown	Inflammation (Deshmane et al., 2009)	unknown
CTRP-4 (C1QTNF4)	NM_031909. Chr 11	Predicted. XM_004941560. Chr 5	55 and 60%	Modulate fat metabolism (Sarver et al., 2020)	unknown
FGF-21	NM_019113 XM_005258731. Chr 19	unknown	unknown	Metabolism (Feve et al., 2016)	unknown
Neuregulin-4	NM_138573. Chr 15	NM_001030544 XM_413738 XR_001464342. Chr 10	58 and 70%	Glucose and lipid metabolism (Wang et al., 2019)	unknown
NOV (Nephroblastoma O Verexpressed gene)	NM_002514. Chr 8	NM_205268. Chr 2	66 and 71%	Tissue repair, inflammation and insulinoreistance (Martinerie et al., 2016)	unknown
Adipsin (complement factor D)	BC057807. Chr 19	Predicted XM_003642860. Chr 28	60 and 65%	Immunity and protect beta cells in case of diabetes (Gómez-Banoy et al., 2019)	unknown
Acylation-stimulating protein (Complement C3)	NM_000064. Chr 19	NM_205405 XM_001236913. Chr 30	53 and 65%	Immunity, metabolism and neurodegeneration (Jian-bin Su et al., 2020)	Potential role in immunity Jiang et al., (2021)
HGF (Hepatocyte Growth Factor)	NM_000601. Chr 7	NM_001030370 XM_415976. Chr 1	74 and 76%	Myocardial and metabolism function (Oliveira et al., 2018)	unknown
LIF (leukemia inhibitory factor)	M63420, J05436. Chr 22	Predicted. XM_425293. Chr 15	38 and 58%	Numerous physiological processes including regulation of cell differentiation, renewal and survival (Wrona et al., 2021)	unclear
Glypican (heparan sulfate proteoglycan)	NM_002081. Chr 2	NM_001305060 XM_422590. Chr 9	60 and 67%	Insulin resistance and adipocytes differentiation (Leelalertauw et al., 2017)	unknown
CCL5/RANTES	DQ230537. Chr 17	NM_001045832 XM_415714. Chr 19	55 and 62%	Mediator of inflammation (Kranjc et al., 2019)	unknown
Angiopoietin-1	AY124380. Chr 8	NM_001199447 XM_418382. Chr 2	92 and 84%	Angiogenesis and regulator of inflammation (Gutbier et al., 2018)	Angiogenesis Drenkhahn et al. (2004)
PCSK9	EF692496. Chr 1	Predicted. XM_025153036. Chr 8	58 and 67%	Modulator of LDL metabolism (Vekic et al., 2019)	unknown

α , secreted as a homotrimer with a molecular mass of 52 kDa, is a pleiotropic inflammatory cytokine produced by macrophages/monocytes during acute inflammation that is involved in different events leading to apoptosis (Hehlgans and Pfeffer 2005). TNF- α gene was cloned in several mammalian species whereas it appeared to be missing in avian species. However, by using very large Illumina sequence datasets, Rohde et al., 2018 were able to assemble a gene which showed significant homology to TNF- α and they further characterize it as a true ortholog by its genomic structure and its biological properties (Rohde et al., 2018). Like leptin, this gene was difficult to identify because of extreme GC-content (~70%), its location in genomic regions with low complexity repetitive and palindromic sequence elements, relatively low sequence conservation and low levels of expression. The chicken TNF profile of mRNA expression resembles that in mammals except for low abundance in the adipose tissue (Seroussi et al., 2016). According to the TNF alpha expression profile and those of its receptors, chicken TNF could be involved not only in the immune system, but also in general cell survival, which is among its classical roles in mammals (Seroussi et al., 2016). However all these suggestions remain to be validated.

6. Hypotheses to explain why mammal adipokines including CCL2, omentin, FGF21 and resistin are still missing in the chicken genome model

Two possibilities could explain the absence of at least four adipokines (CCL2 (C-C Motif Chemokine Ligand 2), omentin, FGF21 (fibroblast growth factor 21) and resistin) in public chicken omics:

Firstly, an adipokine gene could be emerged from the common ancestor genome of theria species (mammal and marsupial species) and consequently it could be absent in the genomes of all other vertebrates. This is a priori the case of the CCL2 gene that is fully absent in transcriptomic and genomic data of fish, amphibian, and sauropsida species. CCL2, also known as monocyte chemoattractant protein-1 (MCP-1) is a pro-inflammatory adipokines secreted by adipocytes. It is 76 amino acids long in humans. It is primarily involved in the regulation of the inflammatory processes (Dommel et al., 2021). However, it also intervenes in the regulation of the metabolism since it impairs insulin signalling in skeletal muscle cells activation at doses similar to its physiological plasma concentrations (200 pg/ml) (Chandrakala et al., 2012).

Secondly, the adipokine genes could be absent in transcriptomic and genomic data because of limits of Illumina and single-molecule real-time (SMRT; PacBio or MINION) methods for making libraries and sequencing them. Such problems were met for at least chicken genes including leptin and TNF α (Beauclair et al., 2019). They were due to certain sequence features of these genes: an elevated GC content (>65%), the presence of G-quadruplexe (G4) and I-DNA motifs that fold in secondary intradyadic structure which are reluctant to replication by DNA polymerases and reverse transcriptases, and the presence of introns and 5' and 3' regions mainly containing G-rich tandem repeats (Beauclair et al., 2019). By ignoring these technical issues, missing genes in genome and transcript models were often considered in the literature as resulting from evolutionary gene losses and adaptations in birds (Dakovic, et al. 2014; Lovell et al., 2014; Zhang et al., 2015), but also in mammals (Sharma et al., 2018). Thanks to the B10K project and to the vertebrate genomes project (VGP), an increasing amount of new data and transcript models are released in databases and numerous missing genes were currently found in each species and-or sibling species. This is the case of omentin and FGF21 genes that can be found in recently released sequences corresponding to mRNA and genomic contigs of all reptile species so far sequenced and in a few avian species (Table 2). Omentin, also known as intelectin-1 (ITLN-1), is an adipokine with anti-inflammatory and insulin-sensitizing effects (Watanabe, et al. 2017). It is 314 amino acids long in humans. Despite some discordant results, serum omentin levels have been shown to be inversely related to obesity and to increase after weight loss. Fibroblast growth factor 21

Table 2

Sequence data samples supporting the presence of adipokines and GLUT4 genes missing in the chicken omics models.

Gene names	Evidence in reptile species (Acc N°, species, type of nucleic acid, GC content)	Evidence in avian species (Acc N°, species, type of nucleic acid, GC content)
Resistin	XM_037884177, <i>Chelonia mydas</i> , predicted mRNA, 62.4% XM_015417997.1, <i>Gekko japonicus</i> , predicted mRNA, 49% XM_033139658.1, <i>Lacerta agilis</i> , predicted mRNA, 47.8% XM_034408746.1, <i>Pantherophis guttatus</i> , predicted mRNA, 40.7% XM_020796295.1, <i>Pogona vitticeps</i> , predicted mRNA, 48.2% AKHW03004588, <i>Alligator mississippiensis</i> , gDNA, 60% NW_006709926.1, <i>Chelonia mydas</i> , gDNA, 61.5% NW_007281833.1, <i>Chrysemys picta bellii</i> , gDNA, 60% NW_005857693.1, <i>Pelodiscus sinensis</i> , gDNA, 63.4% NC_048313.1, <i>Trachemys scripta elegans</i> , gDNA, 60.3%	currently not identified and expected to display GC content above 60% in all species
Omentin	XM_006038928, <i>Alligator sinensis</i> , predicted mRNA, 57.1% XM_037882988.1, <i>Chelonia mydas</i> , predicted mRNA, 57.7% XM_015408331.1, <i>Gekko japonicus</i> , predicted mRNA, 50.6% XM_033174982.1, <i>Lacerta agilis</i> , predicted mRNA, 53.7% XM_020810228.1, <i>Pogona vitticeps</i> , predicted mRNA, 48.7%	XM_026079118.1, <i>Apteryx rowi</i> , predicted mRNA, 66.1% XM_026111569.1, <i>Dromaius novaehollandiae</i> , predicted mRNA, 68.2% XM_026043248.1, <i>Nothoprocta perdicaria</i> , predicted mRNA, 68.3% XP_010211902.1, <i>Tinamus guttatus</i> , predicted mRNA, 65.36% VWPX01014742.1, <i>Crypturellus soui</i> , gDNA, 67.3% XM_021383170.1, <i>Numida meleagris</i> , predicted mRNA, 62.8% SPOS01000447.1, <i>Centrocercus minimus</i> , gDNA contig, 66.1% VWPW01023652.1, <i>Crypturellus undulatus</i> , gDNA contig, 75.9% BJCA01006659.1, <i>Lagopus muta japonica</i> , gDNA contig, 62% QCWP01025761.1, <i>Phasianus colchicus</i> , gDNA contig, 60.9%
FGF21	XM_016996707.1, <i>Anolis carolinensis</i> , predicted mRNA, 43.4% XM_027819103.2, <i>Chelonia mydas</i> , predicted mRNA, 63.6% XM_005289475.2, <i>Chrysemys picta bellii</i> , predicted mRNA, 64.8% XM_033170961.1, <i>Lacerta agilis</i> , predicted mRNA, 52.6% XM_034791796.1, <i>Trachemys scripta elegans</i> , predicted mRNA, 63.5%	
GLUT4	XM_037888888.1, <i>Chelonia mydas</i> , predicted mRNA, 55.1% XM_005279356.2, <i>Chrysemys picta bellii</i> , predicted mRNA, 55.9% XM_015420346.1, <i>Gekko japonicus</i> , predicted mRNA, 56.2% XM_030548144.1, <i>Gopherus evgoodei</i> , predicted mRNA, 55.2% XM_006112124.3, <i>Pelodiscus sinensis</i> , predicted mRNA, 57.1%	currently not identified and expected to display GC content above 60% in all species

(FGF 21) is a protein consisting of 155 amino acids in humans. It is a unique FGF with metabolic, but not proliferative activities. FGF21 is abundantly expressed in the liver but it is also an adipokine in mammals (Feve et al., 2016). FGF21 produced in WAT enhances the expression of adiponectin in WAT as well as serum adiponectin levels. FGF21 is still missing in the avian genome. The characteristic of omentin and FGF21 sequences is that all display elevated GC contents and densities in G4 and I-DNA motifs.

Concerning the resistin gene, it is found in databases to be ubiquitous in reptile species that displayed elevated GC content. Because the sequences of the leptin, TNF α , omentin, and FGF21 genes display GC contents significantly more elevated in avian genome than in those of reptiles, the issues about the existence of a resistin gene in bird must be

carefully considered, but it can be expected that the chicken resistin gene displays a high GC content if it exists. In the context of this review, a similar consideration must be accounted for the GLUT4 gene that is ubiquitous in reptile species so far sequenced and displays an elevated GC content (>56%) (Table 2).

7. Conclusions

In conclusion, all mammalian adipokines are not yet described in avian species. Furthermore, some of these mammalian adipokines have different tissue distributions and consequently probably exert different roles in chicken. However, most of the studies reported expressional data at the mRNA levels and very few at the protein levels. Thus, in terms of tools and technological progress, it appears very important to develop specific avian tools such as adipokine arrays or adipokine multiplex assays to measure plasma adipokines (and for some adipokines such as adiponectin and chemerin to be able to measure specific forms) and to precisely investigate the role of the adipokines in birds. Also, the development of the genome editing technology in chicken could lead to better understanding of the roles of adipokines in specific avian tissues or cells.

Several reports in chicken as in mammals showed that adipokines including adiponectin, visfatin, chemerin and adipokine receptors (AdipoR1, AdipoR2, CMKLR1 ...) are expressed not only in adipose tissue but also in ovary and testis suggesting autocrine/paracrine and endocrine effects. Furthermore, these adipokines could be used as potential biomarkers of metabolic and reproductive physiology and pathology. Concerning the physiological processes, Zuidhof (2018), Baxter and Bédécarrats (2019) suggested that sexual maturity is not exclusively triggered by photoperiodic cues, but rather hens are required to reach a critical threshold in body weight or fat composition in order to enter lay (Zuidhof, 2018; Baxter and Bédécarrats, 2019). Thus, adipokines could participate to this parameter of enter lay that is economically important for the breeders. In addition, in hen broiler, adipokines could be involved in the disorganisation of follicular hierarchy in response to *ad libitum* feeding. Concerning the pathological events, in human, higher body mass index is associated with reproductive disorders including polycystic ovary syndrome (PCOS) and an increase in ovarian cancer risk in women. The chicken is a unique experimental model to investigate the spontaneous onset and progression of ovarian cancer (OVC) (Hawkrige, 2014). In hens, the prevalence of OVC can range from 10 to 35% (Hawkrige, 2014). In chicken, Tiwari et al. showed that plasma adiponectin levels may not be predictive of advanced stages of ovarian tumor (Tiwari et al., 2015). However, the involvement of the other adipokines in OVC remain to be studied.

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