12 Vitellogenin Receptor in Fishes

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Abstract

The main component of the yolk of vertebrate eggs is vitellogenin. As essential nutrients for developing embryos, all fishes produce vitellogenins. The majority of the components required to create and support a new life are delivered to the ooplasm of oocytes by vitellogenin when they develop by orders of magnitude during oogenesis. Vitellogenin is a complex glycophospholipoprotein in the blood of mature female fishes produced by the liver in response to circulating estrogen, released into the bloodstream and taken up by growing oocytes, and chemically modified to form a suite of egg yolk proteins. Vtg is unique to mature females, hence measuring vitellogenin expression or plasma levels is thought to be a helpful method for assessing female maturity in relation to changes in peripheral gonadal steroid levels. Nevertheless, yolk precursor proteins can be found in males or juveniles exposed to estrogens. This protein is typically not detectable in males or juveniles.

Keywords
Vertebrate · Steroid · Oogenesis · Ooplasm · Receptor

12.1 Introduction

Hepatic production and bloodstream secretion of vitellogenin are key components of vertebrate vitellogenesis. Pan et al. (1969) suggested the word vitellogenin to describe the female-specific blood-borne yolk precursors seen in insects. The term

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vitellogenin has mainly been accepted to denote yolk precursor proteins found in the blood of oviparous vertebrates. Subsequently, the same sort of yolk precursors have been reported in many different phyla. The majority of taxa, including teleost fishes, amphibians, and reptiles (Morini et al. 2020), have a single protein called vitellogenin that is present in the blood. Oocyte growth in oviparous species is dependent on the uptake of nutrients and their storage as yolk, whose constituents are subsequently used by the embryo during early stages of its development. One of the most varied groups of vertebrates is the teleosts. Their capacity to use different reproductive systems to fill a variety of ecological niches has been a key factor in their success. These reproductive systems are behavioral as well as biological. Different gender differentiation, fertilization techniques, and the quantity of spawning cycles are all features of biological systems. Mating systems and parental care are examples of behavioral systems.

12.2 Vitellogenin in Fishes

A complex glycol-phospho-lipoprotein called vitellogenin is created by the liver in response to circulating estrogen in the blood of mature female fishes. It is then released into the bloodstream, taken up by developing oocytes, and chemically changed to form a group of egg yolk proteins (Specker and Sullivan 1994). Vitellogenin makes its way through multiple cellular and extracellular layers surrounding the oocyte from the capillary network displacing blood at the periphery of the follicle. After penetrating the vitellogenin reaches the oolemma by passing along the oocyte microvilli and internalized through specific cell surface receptors. The synthesis of vitellogenin in hepatocytes has been vastly studied and is well demonstrated to be under the control of estradiol through esterogen receptors.

Receptors that transport vitellogenin into oocytes are of pivotal significance to egg-laying animals since they mediate a key step in oogenesis. In order to satisfy the avid demand of the developing oocytes for circulating vitellogenin, precise mechanisms must have evolved to assure efficient incorporation of vitellogenin. The knowledge of the vitellogenin receptor system in fish is very scarce compared to birds, amphibians, and invertebrates. The piscine receptor for vitellogenin was first characterized in the ovary of coho salmon, *Oncorhyncuskysutch* (Stifani et al. 1990). Later specific receptors for vitellogenin were identified in rainbow trout *Oncorhynchus mykiss* (Rodriguez et al. 1996). Though the vitellogenin-specific receptors are highly conserved between species, specific characteristics are there for different species that contain species with different reproductive strategies. The information on vitellogenin receptor system will be necessary to understand the mechanisms regulating oocyte growth in fish.

In fish, the vitellogenin is specifically incorporated into oocytes by receptor-mediated endocytosis at specific areas known as coated pits (Barber et al. 1991). In fishes, vitellogenin (Vg) binds to a specific receptor (VgR) on the oocyte surface and is then sequestered via receptor-mediated endocytosis. A membrane receptor on the oocyte surface with a high affinity for Vg, called the Vg receptor (VgR), mediates the endocytotic process. Ooytes sequester vitellogenin through a process of receptor-mediated endocytosis. There is specific binding of vitellogenin to fish ovarian membrane preparations using a salmonid species to confirm the existence of a receptor-mediated system for vitellogenin internalization in fishes. The salmon vitellogenin receptor was found to resemble the vitellogenin receptor of chicken and Xenopus with regard to its estimated mass, binding kinetics, ligand specificity, and localization to the ovary (Tyler and Lancaster 1993; Rodriguez et al. 1996).

12.3 Vitellogenin Receptor in Fishes

The vitellogenin receptor (VTGR), which is also found in non-oviparous vertebrates like humans, is essential for oocyte development in egg-laying mammals. The primary source of nutritional reserves for the growing ebryos is the integration and proteolytic cleavage of vitellogenin into oocytes. The VTGR, also known as very-low-density lipoprotein receptor (VLDLR), is a member of the low-density lipoprotein receptor superfamily (LDLR). The low-density lipoprotein receptor (LDLR) family includes the vitellogenin receptor (Hussain et al. 1999). Members of the LDLR family are involved in lipid metabolism in both vertebrates and invertebrates by binding a variety of ligands.

In teleosts, the vitellogenin receptors have been described including, for example, rainbow trout, *Oncorhynchus mykiss* (Prat et al. 1998), white perch, *Morone americana* (Hiramatsu et al. 2002), cutthroat trout, *Oncorhynchus clarkii* (Mizuta et al. 2017), or in eels. In fish, the molecular weight of the vitellogenin receptors for coho salmom (*Oncorhyncus kisutch*) 100 kDa (Stifani et al. 1990), common carp (*Cyprinus carpio*) 90 kDa (Le Menn and Núñez Rodriguez 1991), and rainbow trout (*Oncorhynchus mykiss*) 200 kDa (Tyler and Lancaster 1993).

Generally, circulating vitellogenin forms a complex with the vitellogenin receptor at the plasma membrane of oocytes (Wall and Patel 1987). Internalized as coated vesicles into the cytoplasm is the vitellogenin receptor complex. The mature yolk protein is created from vitellogenin in the end, and the receptor for vitellogenin is then attracted to the cell membrane via tubular vesicles. Hence, the vitellogenin receptor is essential for fish oogenesis, which is further demonstrated by data that genetic deletions or mutations of the receptor could impede or cause aberrant ovarian development as well as, occasionally, female sterility. Five highly conserved structural domains make up the vitellogenin receptor: the ligand-binding domain, the EGF precursor homology domain, the O-linked sugar domain, the transmembrane domain, and the cytosolic domain (Tufail and Takeda 2009).

The most dominant trigger of vitellogenin expression is the ovarian steroid hormone 17β-estradiol (E2) that is synthesized under the regulation of the hypothalamic–pituitary–gonad axis (Polzonetti-Magni et al. 2004). The evidence available thus far supports the hypothesis that particular nuclear estrogen receptors serve as the primary mediators of estrogen activity (ERs). Using estrogen receptors on the hepatocytes, the estrogen acts on the vitellogenin gene in the nucleus by attaching to sex steroid hormone-binding globulin in the blood. Hepatocytes' combination of estrogen and the oestrogen receptor attaches to the vitellogenin gene's promoter region and activates it to start and speed up transcription. Blood vitellogenin enters the cell after binding to the vitellogenin receptor on the oocyte plasma membrane. Circulating estradiol travels into the liver cells and attaches to an esteradiol receptor, causing a conformational shift and dimerization. The vitellogenin gene's protmoter region contains incomplete esterogen receptor sequences or esterogen response elements, which the dimerized complexes bind to to start the gene's expression and produce vitellogenin.

Estrogens diffuse into the cell during this process and bind to ERs, which are found in the cytosol or nucleus of the target cells. The ERs form homo- or hetero dimers after ligand interaction, and these dimers bind to particular palindromic estrogen response elements (ERE) sequences (Gruber et al. 2004) in the promoter region of estrogen-responsive genes, resulting in recruitment of coactivators or corepressors to the promoter. This results in altered quantities of mRNA and related protein synthesis, which triggers the physiological response. (Kinge et al. 2004). In teleosts, there are several forms of esterogen receptors. Three esterogen receptor ER subtypes were described so far for fish and include the estrogen receptor 1, estrogen receptor 2b, and estrogen receptor 2a [with the gene names of estrogen receptor 1 (esr1), estrogen receptor 2b (esr2b), and estrogen receptor 2a (esr2a), respectively) (Menuet et al. 2002; Hawkins et al. 2000)]. The term "nongenomic activities" refers to some of estrogens' effects that happen so quickly that they cannot rely on RNA and protein synthesis. They entail triggering protein-kinase cascades, which ultimately result in the phosphorylation and activation of transcription factors (TFs) in the nucleus, regulating gene expression. Vitellogenin is strictly regulated by E2-dependent up-regulation of esr1 expression in the liver. Vtg is unique to mature females, hence measuring vitellogenin expression or plasma levels is thought to be a helpful method for assessing female maturity in relation to changes in peripheral gonadal steroid levels. Nevertheless, yolk precursor proteins can be found in males or juveniles exposed to estrogens. This protein is typically not detectable in males or juveniles.

Since E2 stimulation increases hepatic ER1 mRNA expression, esterogen receptor 1 appears to be crucial for the transcription of vitellogenin genes (Mushirobira et al. 2018). The complexes are endocytosed in clathrin-coated pits that invaginate to form coated vesicles after vitellogenin binds to their receptors. These endocytosed vesicles form multivesicular structures when they fusion with lysosomes in the peripheral ooplasm. The proteolytic enzyme cathepsin D is present in the lysosomes, and it is possible that other enzymes (like cathepsin B) colocalize with the imported vitellogenins. When the pH of multivesicular structures drops, catepsin D is activated and cleaves vitellogenin into yolk proteins, which are then stored as yolk granules, globules, platelets, or as liquid yolk in the ooplasm (Romano et al. 2004). The isolation of a cDNA encoding for the trout oocyte Vtg receptor led to the identification of the receptor's site of production. As shown by in situ hybridization experiments, transcripts are not found in ovarian somatic cells and are exclusively found in oocytes and the absence of transcripts from oocytes during their phase of rapid growth, when receptors are absorbing Vtg at the highest rates.

12.4 Conclusion

Regulation of Vtg receptor gene expression has potential commercial implications in addition to scientific ones, at least in fishes. Additionally, vitellogenesis has been suggested as a biomarker system for estrogenic contamination of the aquatic environment.

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