Gynecological Endocrinology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/igye20

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To cite this article: Antonio La Marca, Serena De Carlini & Francesca Liuzzi (2023) Vasorin: a new molecule in human reproduction?, Gynecological Endocrinology, 39:1, 2273282, DOI: 10.1080/09513590.2023.2273282

To link to this article: https://doi.org/10.1080/09513590.2023.2273282

GYNECOLOGICAL ENDOCRINOLOGY
2023, VOL. 39, NO. 1, 2273282
https://doi.org/10.1080/09513590.2023.2273282

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EDITORIAL

Vasorin: a new molecule in human reproduction?

Vasorin was first identified from a mouse kidney cDNA library in 2002 (Slitl2) [1]. The murine gene was originally named Slit-like 2 (Slitl2) due to its structural similarities with the eponymous Slit proteins [2]. The gene locus consists of two exons spanning over a region of approximately 11 kb on chromosome 16. The coding region translates into a typical single-pass type I transmembrane protein of 673 amino acids with a molecular weight of 72 kDa.

The extracellular amino-terminus contains a putative signal peptide, a combination of leucine-rich repeat regions and epidermal growth factor domains (regions conserved within the Slit family of proteins), and a fibronectin type III domain. These motifs are followed by a highly hydrophobic transmembrane domain and by a short intracellular carboxy-terminus. Vasorin is a highly-conserved gene and its orthologs have been identified in numerous other species, including the rat (*Rattus norvegicus*), zebrafish (*Danio rerio*), chicken (*Gallus gallus*), and man (Homo sapiens). The alignment of the mouse Slitl2 full-length sequence reveals an overall identity of more than 95% and 83% at the amino acid level with the rat and the human homolog, respectively [3].

In 2004, Ikeda et al. [4] published the first study reporting the localization of Vasorin in adult human tissues, highlighting its role in the regulation of the activity of Transforming Growth Factor Beta (TGF-β) activity. The TGF-β superfamily consists of a structurally conserved group of proteins that act as extracellular ligands in several physiological and pathological processes, such as cell proliferation, differentiation, apoptosis, cell migration, cancer, cardiovascular disease, fibrosis, and skeletal disorders. Ikeda et al. showed that the down-regulation of Vasorin induced by acute vascular injury in the vascular smooth muscle cells contributed to the fibroproliferative response to vascular damage by counteracting the TGF-β signaling through the direct binding of the extracellular domain of Vasorin to TGF-β family members [4].

Following these findings, Malapeira and colleagues demonstrated that only the soluble form of Vasorin acts as a trap for TGF-β and that the secretion of Vasorin is closely controlled by the metalloprotease ADAM17 [5]. In 2011, Choksi et al. [6] described Vasorin as a HIF-1 target protein named ATIA (anti-TNFα induced apoptosis), which protects cells against TNFα- and hypoxia-induced apoptosis by suppressing reactive oxygen species (ROS) production. In addition to being localized on the cell membrane and being secreted, this study showed that Vasorin may be localized in the mitochondria where it exerts its anti-apoptotic function modulating the function of thioredoxin-2 [6].

Vasorin's link with the TGF-β pathway has more recently led to an analysis of its involvement in tumorigenesis. Vasorin has in fact been reported to be upregulated in some types of human tumors, including hepatocellular carcinoma, breast cancer and glioblastoma, where it plays a key role in tumor progression and angiogenesis. In addition, it has also been identified in thyroid and colorectal cancer as a potential biomarker that regulates the epithelial-mesenchymal transition by activating YAP/TAZ and PI3K/AKT signaling pathways [7–11].

As reported so far, Vasorin is thus mainly being investigated for its involvement in pathological conditions and not much knowledge is currently available regarding its physiological role. One exception is represented by the study of Rimon-Dahari et al. [12] that in 2018, along the idea of the central role of TGF-β in ovarian physiology, explored in a mouse model system the role of Vasorin in folliculogenesis. The study demonstrated that Vasorin was expressed by the granulosa cells, and that its expression was upregulated by LH. Furthermore, the enhanced ovulatory response in the Vasorin cKO mice has been associated with the overactivation of the TGF-β signaling pathway and a lower number of atretic antral follicles [12]. For the first time, this study has therefore identified Vasorin as a new regulator of murine folliculogenesis by participating in the regulation of antral follicle survival, and the establishment of the ovarian follicle pool. The fact that Vasorin is evolutionary conserved between mice and primates suggests that similar roles for Vasorin may also be observed in the human ovary. In view of this, and considering the well-described role of Vasorin as both an inhibitor of TGF-β signaling and an antiapoptotic factor suppressing ROS production, our interest is currently focused on investigating the potential role of Vasorin in human reproduction.

In fact, both TGF-β and ROS have a profound impact on fertility and the reproductive function. Members of TGF-β family such as TGFβ1, TGFβ2 and TGFβ3 are abundant in mammalian reproductive tissues where they are involved in gonad and secondary sex organ development, spermatogenesis and ovarian function, immunoregulation in pregnancy, embryo implantation and placental development [13].

Likewise, physiological amounts of ROS play an important role in the normal reproductive function acting as second messengers in most signal transduction pathways involved in follicular development, ovulation, sperm capacitation, corpus luteum formation and luteolysis, decidualization, early embryo development, and maintenance of pregnancy. On the other hand, persistent and elevated ROS generation leads to oxidative stress. The role of oxidative stress in human reproduction is becoming increasingly important, since it is implied in the aetiopathogenesis of many female reproductive dysfunctions such as, endometriosis, spontaneous abortions, preeclampsia, embryopathies, and preterm labor. In addition, ROS can also promote detrimental changes during spermatogenesis, epididymal maturation, and sperm capacitation leading to male infertility [14,15].

In the light of these considerations, our research is currently ongoing to investigate in both female and male reproductive system the presence of Vasorin and its potential role as a modulator of the TGF-β pathway and ROS production. In this regard, we have recently reported first evidence for the expression of Vasorin in the human female reproductive tissues revealing its presence

in the ovary and the endometrium [16]. Our *in vitro* analyses located the protein on the cell surface of granulosa and endometrial stromal cells, thus setting the basis for further investigation to establish the function and molecular mechanisms by which Vasorin acts in the human female reproductive system. These functional studies could thus have translational value by opening the perspective to explore in future studies the potential therapeutic implications of modulating Vasorin activity in the context of reproductive health.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Received 11 September 2023; revised 11 October 2023; accepted 16 October 2023
Published online 27 October 2023