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Review

The emerging role of follistatin under stresses and its implications in diseases

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ABSTRACT

Follistatin (FST), a single-chain glycosylated protein, is expressed in various tissues. The essential biological function of FST is binding and neutralizing transforming growth factor β (TGF-β) superfamily, including activin, myostatin, and bone morphogenetic protein (BMP). Emerging evidence indicates that FST also serves as a stress responsive protein, which plays a protective role under a variety of stresses. In most cases, FST performs the protective function through its neutralization of TGF-β superfamily. However, under certain circumstances, FST translocates into the nucleus to maintain cellular homeostasis independent of its extracellular antagonism activity. This review provides integrated insight into the most recent advances in understanding the role of FST under various stresses, and the clinical implications corresponding to these findings and discusses the mechanisms to be further studied.

1. The biological function of FST

Follistatin (FST) was first isolated from ovarian follicular fluid in 1987 as a specific inhibitor of follicle stimulating hormone (FSH) by Robertson and Ueno (Robertson et al., 1987; Ueno et al., 1987). FST gene has been localized on human chromosome 5 encoded by a relatively small region of ~6 kb. FST gene contains six exons separated by five introns, with an alternative splicing site where two major FST isoforms were produced, FST288, and FST315. A third isoform, FST303, appears to be derived from proteolytic cleavage of FST315. All the three FST isoforms embrace a residue N-terminal domain and three 10-cysteine FST domains (FDs), termed FSD1, FSD2 and FSD3 (Phillips and de Kretser, 1998; Keutmann et al., 2004).

As a multifunctional regulatory protein, the primary function of FST is the antagonism effect on transforming growth factor β (TGF-β) superfamily, including activin, myostatin, and bone morphogenetic protein (BMP). As secreted factors, TGF-β family members stimulate signal transduction through type I and II receptors. The canonical activin signaling pathway involves an activin dimer binding to type I and type II receptors, which ultimately leads to phosphorylation of the type I receptor. This receptor then phosphorylates the second messenger molecules Smad2 and Smad3 that, once activated, complex with a common Smad4. This complex then translocates to the nucleus where it activates gene transcription (Xia and Schneyer, 2009). Myostatin receptors also use Smad2/3 for its signaling transduction (Rodriguez et al., 2014). However, the activation of BMP receptor phosphorylates Smad1/5/8, which mediates Smad4 recruitment and nuclear translocation (McDowall et al., 2008). Mutation studies have shown that the N-terminal domain and the first two FDs are found to be critical for activin binding (Keutmann et al., 2004). The structure of the FST:activin complex revealed that two FST molecules encircle activin, covering a large percentage of the surface and completely blocking both type I and type II receptor binding sites (Thompson et al., 2005). Through neutralization of TGF-β superfamily, FST participates in various processes such as cell growth, development, and differentiation.

2. The role of FST under stresses

All living organisms undergo various ranges of environmental stresses, including oxidative stress, nutritional deficiency, hypoxia and so on. In response to stressors, cells conduct a multitude of molecular changes to protect cells against unfavorable environmental conditions, called cellular stress response. During cellular stress response, a series of stress responsive proteins are selectively expressed, which play essential roles in promoting the survival of cells. Evidence has shown that the expression of FST is up-regulated during a series of stresses

Abbreviations: FST, follistatin; TGF-β, transforming growth factor β; BMP, bone morphogenetic protein; FSH, follicle stimulating hormone; FD, FST domain; ROS, reactive oxygenated species; NOX, NADPH oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; EoE, eosinophilic esophagitis; NLS, nuclear localization signal; IR, ionizing radiation; OS, oscillatory shear stress; ARE, AU-rich element

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including oxidative stress and glucose deprivation. FST plays a protective role under most of these stresses, indicating that FST is a stress responsive protein. Based on the pivotal role of this protein, it is not surprising that dysregulation of FST was observed in the development of diseases.

2.1. The role of FST under oxidative stress

Oxidative stress is the consequence of an imbalance between production and elimination of reactive oxygenated species (ROS) which can induce oxidative injury, leading to cell damage subsequently. Oxidative stress is closely related with diseases such as preeclampsia and aging-related diseases (Lopez-Otin et al., 2013; Guerby et al., 2015). Studies have shown that FST reduces ROS production, and dysregulation of FST might induce oxidative stress and promote disease progression.

The case-control study of preeclampsia showed that the level of serum activin in women with preeclampsia is significantly higher than healthy controls (Yu et al., 2011). Inversely, FST serum level in women with preeclampsia is dramatically lower than healthy women (Garces et al., 2015). In cultured human umbilical vein endothelial cells, activin induces ROS production through activating Smad2/3 to increase NADPH oxidase 2 (NOX2) activities, which disturbs endothelial integrity in turn. However, FST could down-regulate NOX2 protein levels to attenuate the production of ROS, which protects endothelial integrity. These studies implicate that activin promotes ROS production and the pathogenesis of preeclampsia, while FST inhibits this process by neutralizing activin (Lim et al., 2015). Taking advantage of its secreting property, FST offers an opportunity for preeclampsia treatment.

Studies have reported an increase of ROS in skeletal muscle during aging (sarcopenia). The elevated ROS promotes cellular protein degradation through ubiquitin-proteasome pathway, which leads to loss of mass in the skeletal muscle (Powers et al., 2005). Myostatin, a negative regulator of muscle growth, is induced in aged skeletal muscle in humans and rodents (Baumann et al., 2003; Raue et al., 2006; Leger et al., 2008). However, FST expression is significantly decreased during aging. On the contrary, aerobic exercise training could up-regulate FST in aged skeletal muscle of male rats, which blocks the activity of myostatin to promote myogenesis (Ziaaldini et al., 2015). In cultured C2C12 myoblasts, myostatin induces the generation of ROS, which is mediated by TNF-α and NADPH oxidase. Higher levels of ROS further triggers muscle wasting (Sriram et al., 2011). This study indicated that myostatin is a pro-oxidant and signals the generation of ROS in muscle cells. As an inhibitor of myostatin, FST might inhibit ROS production and lead to reduced muscle wasting during sarcopenia.

Series of exogenous toxins such as nanoparticles, heavy metal, and H_2O_2 could induce cellular oxidative stress and cell damage (Lin et al., 2016). Recently, we have demonstrated that under silica nanoparticle-induced oxidative stress, FST transcription is induced. Down-regulation of FST promotes silica nanoparticle-induced apoptosis both in cultured cells and in mouse lung tissue. Furthermore, knockdown of FST increases while overexpression of FST decreases the expression level of NADPH oxidase 1 (NOX1) and NOX5 as well as the production of cellular ROS (Lin et al., 2016). These findings further consolidated the protective role of FST during oxidative stresses.

In contrast to the damaging effects of ROS, evidence has shown that ROS at lower, nontoxic levels is important for normal physiological process such as stem cell differentiation (Jang and Sharkis, 2007). In vitro and in vivo studies have shown that bone morphogenetic protein (BMP) activation triggers production of ROS and Nrf2 (nuclear factor erythroid 2-related factor 2) activation, which is required for esophageal basal cell differentiation. BMP antagonist FST inhibits BMP4-induced ROS production and basal cell differentiation. Not surprisingly, increased levels of FST and decreased BMP activation were observed in eosinophilic esophagitis (EoE) mouse model and human biopsies. The up-regulated FST neutralizes BMP and reduces Nrf2 signaling, leading to expansion of basal progenitor during the pathogenesis of EoE (Jiang et al., 2015).

2.2. The role of FST under energy deficiency

Solid tumors over a certain size are continuously exposed to glucose deficiency and hypoxia microenvironments because of the inadequate vascular supply, which will result in cellular energy deficiency. The cancer cells will limit energy expenditure to antagonize these energy-deprived conditions. An effective way is to reduce ribosome biogenesis, the most energy-consuming process in eukaryotic cells. As a matter of fact, cellular rRNA transcription is tightly regulated in response to cellular energy conditions (Moss et al., 2007). Our group has reported that glucose deprivation markedly enhances the expression and nucleolar localization of FST in HeLa cells. The nucleolar localization of FST relies on its nuclear localization signal (NLS) comprising the residues 64–87. FST in the nucleolus negatively regulates rRNA synthesis and ribosome biogenesis to keep cellular energy homeostasis. These functions depend on the presence of an intact NLS because the NLS-deleted mutant of FST lost the rRNA inhibition effect and the cell protective effect (Gao et al., 2010). In support of our findings, nuclear localization of FST was observed in epithelial cells of breast tissue, suggesting a nuclear function of FST (Bloise et al., 2009). Overall, our study identified a novel nucleolar function of FST, which is of importance in the modulation of cancer cell survival in response to glucose deprivation (Fig. 1).

Consistent with our in vitro study, mouse and human studies have also demonstrated that circulating FST level responds to energy metabolic challenges. In human physiology, plasma FST increases in conditions with increased energy demands such as prolonged fasting and acute exercise (Hansen and Plomgaard, 2016; Hansen et al., 2016). Hansen et al. (2011) has also reported that exercise increases mouse plasma FST level and it most likely originated from the liver. It is proposed that these conditions lead to increased glucagon level in combination with reduced insulin level. The increased glucagon-to-insulin ratio stimulates the liver to secrete FST into the circulation (Hansen and Plomgaard, 2016; Hansen et al., 2016).

Ischemic diseases, such as acute myocardial infarction, are also accompanied with acute glucose deprivation and hypoxia. It has been demonstrated that FST administration attenuates the myocardial, renal and hepatic ischemia-reperfusion injury (IRI) (Maeshima et al., 2001; Kanamoto et al., 2011; Chen et al., 2014). FST treatment, through binding and neutralizing the actions of activin B and subsequently activin A, reduced renal IRI by minimizing endothelial cell activation and dampening the systemic inflammatory response (Fang et al., 2016). Although the detailed mechanism is unknown, these studies implicate a protective function of FST in ischemia-reperfusion and may serve as a potential therapeutic target for these diseases.

2.3. The role of FST under other stresses

FST also responds to physical stresses, such as ionizing radiation (IR), and shear stress. IR, usually used for cancer treatment, could result in marked fibrotic response in a normal tissue of patients (Forrester et al., 2013). It was reported that the expressions of both activin A and FST are increased in fibroblasts originating from patients who developed severe radiation-induced fibrosis following radiotherapy and fibroblasts from patients who did not. However, the FST gene expression level in fibrosis patients is lower than controls, suggesting that FST might play a protective role in IR-induced fibrosis (Forrester et al., 2013).

Endothelial cells (ECs) in branched or curved arterial regions are exposed to disturbed flow conditions such as low mean and oscillatory shear stress (OS), which induce inflammation and atherosclerosis. It has been elucidated that OS could induce production of BMP4 in ECs, which increases monocyte adhesivity of ECs, a critical early atherogenic step.