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Review

FOXO1/3: Potential suppressors of fibrosis

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ABSTRACT

Fibrosis is a universally age-related disease that involves nearly all organs. It is typically initiated by organic injury and eventually results in organ failure. There are still few effective therapeutic strategy targets for fibrogenesis. Forkhead box proteins O1 and O3 (FOXO1/3) have been shown to have favorable inhibitory effects on fibroblast activation and subsequent extracellular matrix production and can ameliorate fibrosis levels in numerous organs, including the heart, liver, lung, and kidney; they are therefore promising targets for anti-fibrosis therapy. Moreover, we can develop appropriate strategies to make the best use of FOXO1/3's anti-fibrosis properties. The information reviewed here should be significant for understanding the roles of FOXO1/3 in fibrosis and should contribute to the design of further studies related to FOXO1/3 and the fibrotic response and shed light on a potential treatment for fibrosis.

1. Introduction

Age-related diseases, such as neurodegenerative disorders (Groot et al., 2016; Nopparat et al., 2017), cardiovascular diseases (Buford, 2016) and cancer (Komarova, 2005; Ribezzo et al., 2016), are sharply increasing in accordance with the rapid growth of the elderly population (Bialystok et al., 2016). Fibrosis refers to a universally age-related disease that affects nearly all human organs and is characterized by excessive fibrous connective tissue formation (O'Reilly, 2017). Normal fibrous connective tissue formation is essential for wound healing and organic structural integrity in the short-term (Eming et al., 2014; Lindsey et al., 2015). However, excessive deposition of collagen over a prolonged period of time is considered to be a pathological state associated with the destruction of normal organic structure and, eventually, organ failure. Fibrosis is a common disease observed in nearly all types of organs and tissues, including the heart (Nishiga et al., 2017), lungs (Martinez et al., 2017), liver (Affo et al., 2017), and kidneys (Munoz-Felix et al., 2015). In contrast to the various features of many organs and tissues, fibrotic changes share common pathogenic pathways throughout the entire body (Rockey et al., 2015). An increase in activated fibroblasts that express alpha smooth muscle actin and copious amounts of extracellular matrix (ECM) molecules is a significant feature and fundamental change that accounts for excessive fibrous connective tissue formation. Therefore, inhibition of fibroblast changes is a promising anti-fibrosis strategy (Guo et al., 2016). Forkhead box proteins O1 and O3 (FOXO1/3), as well-established anti-proliferation and pro-apoptosis factors, exert favorable inhibitory effects on fibroblast activation and subsequent ECM production and are promising targets for anti-fibrosis therapy.

Forkhead transcription factors (FOXOs) are named after the Drosophila melanogaster forkhead genes, which include a subfamily that encodes FOXOs (Weigel et al., 1989). Mammalian cells express four FOXO isoforms (FOXO1, FOXO3, FOXO4, and FOXO6). As known from previous studies, different isoforms exert redundant effects and divergent functions in many diseases. FOXO1/3 are the two most extensively studied isoforms and have many effects on multiple diseases, including cardiovascular diseases (Wilhelm et al., 2016), diabetes (O'Neill et al., 2016), cancer (Kumazoe et al., 2016), aging (de

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Magalhaes et al., 2012), and stem cell activity (Mehta et al., 2015). Moreover, FOXO1/3 are important regulators of aging and longevity, which have attracted much attention (Lettieri Barbato and Aquilano, 2016; Salminen et al., 2016; Schaible and Sussman, 2013). FOXO1/3 were shown to be controlled by several upstream molecules and to regulate many downstream proteins (Xin et al., 2017). Notably, FOXO1/3 have the ability to upregulate a series of cell cycle inhibitors and pro-apoptotic targets, which have been confirmed to inhibit fibroblast activation and subsequent fibrosis in many studies (Adachi et al., 2007; Li et al., 2015a).

The focus of the current review is to evaluate the latest research progress regarding the roles of FOXO1/3 in fibrosis. First, a brief overview of the processes of fibrosis and the regulatory roles of FOXO1/3 in fibrotic pathogenesis are summarized. Subsequently, we present the roles of FOXO1/3 in various organs and in tissue fibrosis in the heart, lungs, liver, kidneys, and so on. Moreover, the relationship between FOXO1/3 and inflammation in fibrosis is discussed, and the relationship between FOXO1/3 and fibrosis in aging is evaluated. Finally, we discuss several features of FOXO1/3 actions and provide a potential therapeutic strategy for targeting FOXO1/3. Collectively, this information should serve as a comprehensive repository that should aid in the design of future studies and increase the potential of FOXO1/3 as therapeutic targets for fibrosis.

2. General background on the FOXO family

The FOXO family is the O-subfamily of proteins that belong to the larger family of forkhead transcription factors, which have been regarded as critical regulators of cell fate (Kaletsky et al., 2016; Wilhelm et al., 2016). It has been validated that FOXO1/3/4/6 are the four isoforms that are expressed in mammalian cells. The first three exhibit a high degree of sequence homology, whereas FOXO6 exhibits major structural differences from FOXO1/3/4 (Bullock, 2016). All FOXO isoforms share the same DNA binding specificity (Fig. 1), characterized by a monomeric DNA binding domain that contains three α helices and two characteristic large loops (Kaestner et al., 2000). FOXOs translocate from the cytoplasm to the nucleus and bind to promoters of target genes and modulate their transcription. Depending on the target genes that they transcriptionally promote, the different FOXO isoforms have some common effects and independent functions. When modified at specific amino acid sites (*i.e.*, FOXO1: Ser256 phosphorylation (Gerst et al., 2015), and FOXO3: Thr32 or Ser253 phosphorylation (Bullock, 2016)), FOXOs are inactivated and bind with 14-3-3 proteins, which promote the relocalization of FOXOs from the nucleus to the cytoplasm (Savai et al., 2014).

Multiple pathways have been shown to regulate FOXO activity, mainly through the modification of FOXOs and 14-3-3 proteins at specific sites and by influencing their interaction and nucleocytoplasmic shuttling. FOXO phosphorylation by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway is a typical process that leads to FOXO inactivation (Cui et al., 2012). PI3K phosphorylation by upstream kinases further phosphorylates Akt, which later translocates from the cytoplasm to the nucleus (Lijnen et al., 2010) and phosphorylates FOXOs (Chaves et al., 2014). FOXO phosphorylation promotes their interaction with 14-3-3, which results in the translocation of FOXOs from the nucleus to the cytoplasm and a decrease in their transcriptional activity. In the cytoplasm, phosphorylated FOXOs are more susceptible to degradation by the ubiquitin-proteasome system (Ronnebaum and Patterson, 2010). The role of acetylation modification in FOXO activity is still under debate. The study by Sewastianik and colleagues (Sewastianik et al., 2016) demonstrated that FOXO1 acetylation increases its nuclear translocation and promotes its transcriptional activity in diffuse large B-cell cell lymphomas, while Wang et al. (2014a) suggested that FOXO1 deacetylation by SIRT1 enhances DNA binding and transcription activity in diabetic cardiomyopathy.

The activated FOXOs promote the expression of multiple target genes that regulate various cellular process, including autophagy, cell cycle, apoptosis, *etc*. Activated FOXOs were shown to bind to the promoter region of autophagy-related genes, such as Gabarapl1, Bcl-2/adenovirus E1B 19-kDa interacting protein 3, and autophagy-related 12, and to promote the autophagy process (Kong et al., 2010; Paula-Gomes et al., 2013; Sengupta et al., 2009). Notably, FOXO1/3 are established cell cycle regulators in proliferating cells. FOXO1/3 are able to promote the expression of a series of cell cycle inhibitors, including p21, p27, and p57 (Evans-Anderson et al., 2008; Johnson and Kartha, 2014), leading to cell cycle arrest and inhibiting fibroblast hyperplasia (Pramod and Shivakumar, 2014). Moreover, FOXO1/3 also enhance the expression of apoptosis-related molecules, such as Bim (Liu et al., 2013b), and FOXO1/3 overexpression has been reported to induce fibroblast apoptosis (Wang et al., 2015).

3. Roles of FOXO1/3 during the fibrotic pathogenic process

The fibrotic response is commonly divided into four major phases on the basis of the development process (Rockey et al., 2015). The first phase refers to the initiation of the fibrotic process, driven by primary injury of the organ and tissues. The second phase is the activation of fibrogenic effector cells. Next, the elaboration of ECM is regarded as the

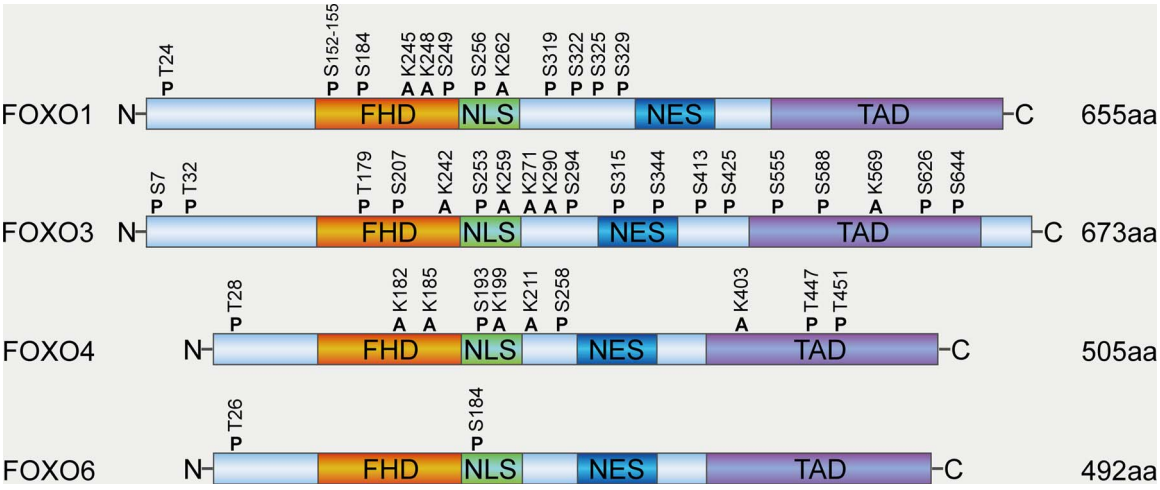

Fig. 1. Schematic of FOXO members. All FOXO isoforms share the same DNA binding specificity, which is characterized by a monomeric DNA binding domain named the FHD. (Abbreviation: A, acetylation site; FHD, Forkhead DNA-binding domain; FOXO, Forkhead box O; K, Lysine; NES, nuclear export sequence; NLS, nuclear localization sequence; P, phosphorylation site; S, Serine; T, Threonine; TAD, transactivation domain).