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Research Progress on Transient Receptor Potential Channels and Myocardial Fibrosis

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Abstract: *Cardiovascular disease seriously endangers human health, and its morbidity and mortality increase year by year, and the incidence population is gradually younger. Myocardial fibrosis is a common pathological outcome of many heart diseases, and it is of great clinical significance to prevent and reverse cardiac fibrosis. Under the influence of various pathogenic factors, the heart eventually leads to the formation of myocardial fibrosis, which in turn leads to heart failure. However, the specific mechanism of myocardial fibrosis formation is unknown. The transient receptor potential channel is closely related to the formation of myocardial fibrosis, and can be targeted to intervene in this channel to play an antifibrotic role. This review elaborates the role of transient receptor potential channels in the formation of myocardial fibrosis, which provides new ideas for clinical treatment and basic research.*

Keywords: *Fibroblast; Myofibroblasts; TGF-β; Ca2+; TRP channel*

1. Introduction

Cardiovascular disease (CVD) seriously endangers human health, according to statistics, in 2019, deaths due to cardiovascular diseases in China accounted for 46.74% and 44.26% of the total deaths in rural and urban areas, respectively, and about two out of 5 people died of cardiovascular diseases [1], as shown in Figure 1. Myocardial fibrosis is a pathological change common to various cardiovascular diseases. Cardiac fibroblasts are the protagonists in the formation of myocardial fibrosis, and their main role is to secrete collagen and other extracellular matrix (ECM). When the heart is damaged, cardiac fibroblasts are stimulated by injury factors to activate into myofibroblasts, and repair the damage by secreting a large amount of extracellular matrix, which if this repair persists, leads to extensive fibrosis of the heart, eventually leading to cardiac structural remodeling, myocardial stiffness, reduced cardiac compliance, heart failure and even death [2]. Transient receptor potential channels (TRP channels) are closely related to the activation of cardiac fibroblasts, and a large number of studies have shown that transient receptor potential channels activate cardiac fibroblasts into myofibroblasts under the action of various induction molecules and promote the process of fibrosis [3]. Ca2+ and transforming growth factor-β1 are key inducers of transient receptor potential channel activation [3].

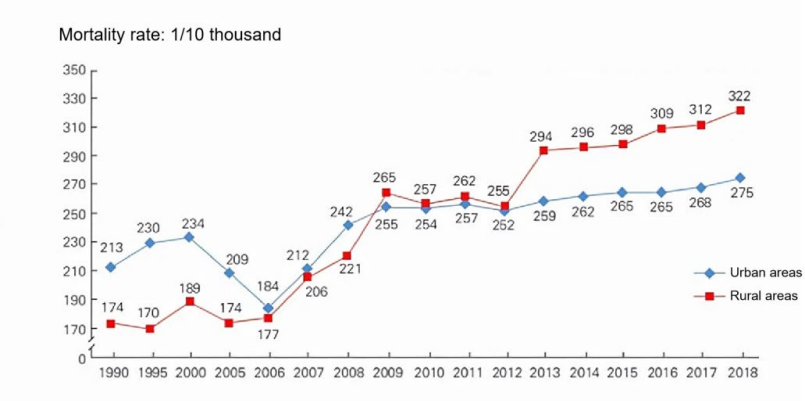

Figure 1: The changes in cardiovascular disease mortality rates among urban and rural residents in China

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2. Structure and function of TRP channels

The TRP channel was originally discovered in the visual system of fruit flies and is named after the transient peak potential produced by genetically mutated fruit flies for sustained light stimulation [4]. The TRP channel is composed of four subunits, each with six transmembrane fragments (S1–S6), forming a pore for cation permeation between S5 and S6, and each subunit amino and carboxyl terminal sites in the cytoplasm participates in the assembly of gated channels and has a variety of sites of interaction with other proteins and molecules [5]. The TRP family consists of 28 members, which are TRPC (Canonical TRPC1-TRPC7), TRPV (Vanilloid TRPV1-TRPV6), TRPM (Melastatin TRPM1-TRPM8), TRPP (Polycystin TRPP1-TRPP3), TRPA (Ankyrin TRPA1), and TRPML (Muco) based on their sequence homology lipin TRPML1-TRPML3) six subfamilies [5], as shown in Figure 2 and Figure 3. The TRP channel is a non-selective cationic transmembrane channel protein located on the cell membrane that has a penetrating effect on Ca2+ and other monovalent cations, except TRPM4 and TRPM5 [6]. When intracellular Ca2+ is depleted, TRP channels are involved in calcium influx [6]. This channel participates in various physiological and pathological processes of the body under the action of various factors inside and outside the cell, such as the formation of fibrosis, oxidative stress, osmotic pressure changes and the metabolism of various substances in the cell [7].

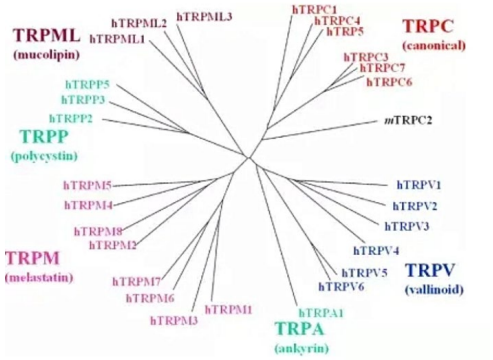

Figure 2: The series of TRP channel

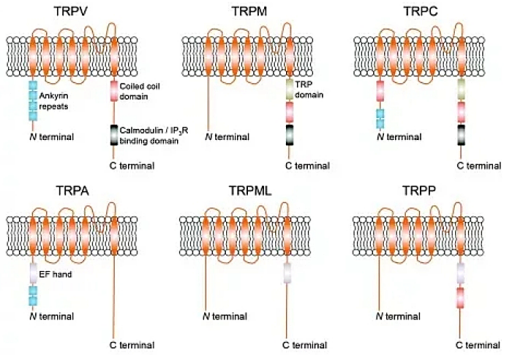

Figure 3: The structure of the TRP channel

3. TRP channels are involved in molecules associated with myocardial fibrosis

3.1. TGF-β1

TGF-β1 is the most critical cytokine in the process of myocardial fibrosis [8]. TGF-β1 binds to TGFβRII and TGFβRI, thereby activating activin receptor-like kinase 5 (ALK5), recruiting and phosphorylating its downstream signaling proteins Smad2 and Smad3, and then translocating into the nucleus to induce gene transcription [9]. In addition, TGF-βI can also activate the MAPK non-classical signaling pathway and regulate cell metabolism [10]. Both the TGF-β1/Smad signaling pathway and the MAPK signaling pathway are involved in myocardial fibrosis by activating cardiac fibroblasts [11]. TRP channels are closely related to the activation of cardiac fibroblasts. TRPV4 has been found to be required

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for TGF-β1-induced differentiation of cardiac fibroblasts into myofibroblasts [12]. Not only in the heart, numerous studies have shown that the TRP channel is indispensable in TGF-β1's involvement in the process of tissue fibrosis. TRPV4 is mediated by the TGF-β1 signaling pathway and ultimately leads to pulmonary fibrosis [13]. In the mouse corneal stroma, the TRPA1 channel is required for TGF-β1 signaling to mediate inflammation and fibrosis after alkaline burns [14]. TGF-β1-mediated excessive intestinal fibrosis is inhibited by inhibition of TRPC6 channels [15]. In conclusion, TRP channel is inseparable from TGF-β1 pathway-mediated myocardial fibrosis, but its specific mechanism of action needs to be further studied.

3.2. Ca2+

Ca2+ signaling regulates a variety of cellular functions and is known to be involved in the activation and proliferation of fibroblasts. Intracellular Ca2+ signaling is mainly released through intracellular Ca2+ storage, and then enters the cell through Ca2+ ion osmosis channels on the cell membrane to participate in important regulatory roles [16]. In recent years, a large number of studies have shown that the physiological activity of cardiac fibroblasts is regulated by the Ca2+ signal within the cell. Ca2+ penetration of cardiac fibroblasts is mainly through non-receptor-activated Ca2+ channels as well as receptor-activated non-selective Ca2+ channels. However, most TRP channels are Ca2+ permeable nonselective cation channels, with the exception of TRPM4 and TRPM5 [17]. In atrial fibrillation goats and dog models, TRPC3 was found to increase its expression under the regulation of Ca2+ signaling, and eventually led to myocardial fibrosis [18]. The TRPC6-mediated Ca2+ signaling pathway has been reported to be required for human cardiac fibroblast proliferation [19]. TRPM7-mediated Ca2+ signaling was found in both cultured human cardiac fibroblasts and mouse cardiac fibroblasts to be crucial in TGF-β1-induced fibroblast proliferation and differentiation [20]. In summary, TRP channel-mediated Ca2+ signaling in cardiac fibroblasts plays an important role in the formation of myocardial fibers.

4. TRP channel and myocardial fibrosis

Myocardial fibrosis is massive deposition of extracellular matrix, resulting to heart hardening, reduced compliance and ultimately heart failure. The extracellular matrix is mainly derived from myofibroblasts. Cardiac fibroblasts are activated to myofibroblasts upon stimulation by various factors. The Ca2+ signaling pathway plays a key role in the proliferation and differentiation of cardiac fibroblasts. TRP channels have been proposed as candidate molecules responsible for Ca2+influx in cardiac fibroblasts. Several TRP channels, including TRPA1, TRPM7, TRPC3, TRPC6 and TRPV4, are functionally expressed in cardiac fibroblasts. Different TRP channels are activated when fibroblasts are stimulated by different stimuli, and mediate Ca2+ entry to support fibroblast proliferation, differentiation to myofibroblasts, and synthesis of extracellular matrix proteins and cytokines. Eventually leads to myocardial fibrosis formation. (Figure 4)

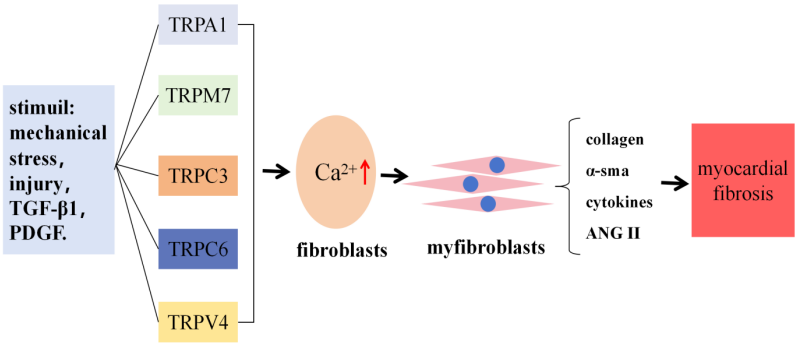

Figure 4: TRP channels and cardiac fibrosis

4.1. TRPA1

TRPA1 is a non-selective cation channel located on the cell membrane with significant channelability to Ca2+ [21]. The TRPA1 channel was first identified on lung fibroblasts [22]. With the in-depth study of this channel, it has been found that the TRPA1 channel is closely related to myocardial fibrosis. For example, HC-030031, a selective antagonist of the TRPA1 channel, can reduce stress overload-induced

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myocardial hypertrophy and myocardial fibrosis in mice by regulating the polarization of macrophages [23]. The TRPA1 channel is required for fibrous repair after myocardial injury [24], and after heart injury, the TRPA1 channel on the cardiac fibroblast membrane is activated, which in turn activates the TGF-β/Ca2+/CaN-NFAT signaling pathway, so that cardiac fibroblasts are activated into myofibroblasts, eventually leading to myocardial fibrosis [22]. The TRPA1 channel was also found to enhance their fibrotic phenotype primarily by mediating Ca2+ entry into fibroblasts. In addition, the TRPA1 channel can also work with the TRPV1 channel to regulate the Ca2+ influx of cardiomyocytes, thereby regulating cardiomyocyte function [25]. In conclusion, the TRPA1 channel plays an important role in the formation of myocardial fibrosis, and inhibiting the activation of this channel may become a new target for the treatment of myocardial fibrosis.

4.2. TRPM7

The TRPM7 channel is not only a cation channel, but also has protein kinase activity due to its serine/threonine protein kinase region at the C-terminus of its structure, so TRPM7 is called a "channelase" [26]. TRPM7 channels are widely distributed in human heart, liver, bone tissue, and adipose tissue. The TRPM7 channel is essential for the maintenance of intracellular Ca2+ and Mg2+ ion homeostasis [27]. TRPM7 was first tracked on cardiac fibroblasts, as the main ion channel for Ca2+ influx on cardiac fibroblasts, which is very important for the expression of profibrosis-related genes in cardiac fibroblasts and the formation of myocardial fibrosis [28]. TGF-β1 upregulated TRPM7 expression in in cardiac fibroblasts cultured in vitro, while silence of TRPM7 significantly inhibited TGF-β1-induced cardiac fibroblast proliferation, differentiation and collagen production [29]. In vivo studies, it was found that inhibition of the expression of TRPM7 channels in the heart tissue of rats with isoprenaline-induced myocardial fibrosis significantly improved myocardial fibrosis in rats [30]. The above evidence suggests that TRPM7 channels play a key role in regulating myocardial fibroblast proliferation, differentiation, and collagen synthesis.

4.3. TRPC3

TRPC3 is a non-selective voltage-gated calcium channel located on the cell membrane that is closely related to calcium depot manipulation calcium influx due to its highly conserved C-terminus of the proline-rich and calmodulin/IP3 receptor-binding region, enabling the channel to function as a multimodal signal [31]. TRPC3, as the only TRPC isotype protein on the cell membrane of the sinus node, is closely related to atrial fibrillation and atrial fibrosis [32]. In TRPC3-specific knockout mice, knockout of this gene inhibits atrial arrhythmias caused by activation of G protein-coupled receptors (GPCRs) Ca2+ signaling [33]. Through clinical electrophysiological data analysis, it was found that in human atrial fibrillation, the upregulation of TRPC3 in fibroblasts is likely to be the cause of atrial fibrillation, which is closely related to myocardial fibrosis [18]. Studies have found that inhibiting the expression of TRPC3 in dog atrial fibrillation models can significantly reduce the proliferation of cardiac fibroblasts and the production of extracellular matrix [34]. In short, TRPC3-mediated Ca2+ overload affects the proliferation and differentiation of atrial myofibroblasts, leading to atrial fibrillation and even atrial fibrotic changes.

4.4. TRPC6

TRPC6 channel is a non-selective cation channel widely present in the heart, mainly expressed in cardiomyocytes, cardiac fibroblasts, vascular endothelial cells and vascular smooth muscle cells. Similar to TRPC3, TRPC6 channels affect cell function mainly by mediating the transduction of Ca2+ signaling, and participate in cardiovascular pathophysiological processes [35]. In vitro cultured cardiac fibroblasts found that TRPC6 can promote cardiac fibrosis during cardiac insufficiency, genome-wide screening determined that TRPC6 expression is required for cardiac fibroblast activation, rat cardiac fibroblasts cultured with TGF-β or Ang II can induce TRPC6 expression with concentration-dependent increase, and silencing or knocking out TRPC6 can inhibit cardiac fibroblast differentiation into myofibroblasts [36]. In in vivo experiments, it was found that BI 749327 could specifically inhibit the expression of TRPC6, thereby inhibiting the expression of related fibrous genes such as collagen I. , collagen III. and TGF-β1 [37]. Thus, inhibition of TRPC6 expression can resist myocardial fibrosis formation.

4.5. TRPV4

The TRPV4 channel is a mechanically sensitive non-selective cation channel that is mainly permeable to Ca2+ ions. TRPV4 not only has a regulating effect on physiological functions such as thermoregulation, osmolality and vasodilation, but also participates in pathological processes such as myocardial fibrosis, myocardial hypertrophy and arrhythmia [38]. In heart failure mice 8 weeks after TRPV4 knockout, it was found that fibrosis in the infarct region was significantly reduced, and more

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surprisingly, there was no fibrosis in the peri-infarct area, further indicating that inhibition of TRPV4 improved ventricular remodeling after myocardial infarction [39]. In vitro studies have found that the silencing of TRPV4 in cardiac fibroblasts by transfection can significantly inhibit the transformation of TGF-β1-induced cardiac fibroblasts to myofibroblasts. These results suggest that TRPV4 regulates the differentiation of cardiac fibroblasts to myoblasts by integrating signaling and mechanical factors from TGF-β1. Similar studies have shown that TRPV4 mediates TGF-β-induced differentiation of human ventricular fibroblasts into myofibroblasts through Ca2+-dependent ERK phosphorylation [12]. A growing body of research shows the important role of TRPV4 in the process of cardiac fibrosis. Suggest TRPV4 as a potential molecular target to mitigate cardiac fibrosis.

5. Conclusion

There are many members of the TRP family, and this article describes a channel closely related to the formation of myocardial fibrosis. In summary, TRP channels are closely related to Ca2+ signaling, and Ca2+ influx is necessary for the proliferation and differentiation of cardiac fibroblasts. Therefore, TRP channels play an important role in the process of myocardial fibrosis. The role of myocardial fibrosis in heart disease is well known, but the treatment of anti-myocardial fibrosis lacks effective methods, which requires new insights and ideas on the underlying mechanism of myocardial fibrosis, so as to provide new therapeutic targets for anti-myocardial fibrosis therapy. This article aims to theoretically provide targets for anti-myocardial fiber drugs by elaborating TRP channels closely related to the formation of myocardial fibrosis and the mechanism of action of each channel participating in myocardial fibrosis.

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