Gene 642 (2018) 1–8

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

The role of TRPV4 in fibrosis

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ARTICLE INFO

Keywords:
TRPV4
Fibrosis
Signaling pathways
Therapeutic target

ABSTRACT

The transient receptor potential vanilloid 4 (TRPV4) is a highly Ca^{2+}-permeable non-selective cation channel in TRPV family. Accumulating evidence hints that TRPV4 play a significant role in a wide diversity of pathologic changes. Fibrosis is a kind of chronic disease which was characterized by the formation of excessive accumulation of extracellular matrix (ECM) components in tissues and organs. In recent years, a growing body of studies showed that TRPV4 acted as a crucial regulator in the progression of fibrosis including myocardial fibrosis, cystic fibrosis, pulmonary fibrosis, hepatic fibrosis and pancreatic fibrosis, suggesting TRPV4 may be a potential therapeutic vehicle in fibrotic diseases. However, the mechanisms by which TRPV4 regulates fibrosis are still undefined. In this review, firstly, we intend to sum up the collective knowledge of TRPV4. Then we provided the latent mechanism between TRPV4 and fibrosis. We also elaborated the distinct signaling pathways focus on TRPV4 with fibrosis. Finally, we discussed its potential as a novel therapeutic target for fibrosis.

1. Introduction

The transient receptor potential vanilloid 4 (TRPV4) channel is a subclass of TRPV ion channels family (Ferreira and Faria, 2016). TRPV4 is well known as a highly Ca^{2+}-permeable non-selective cation channel (Sonkusare et al., 2012; Ying et al., 2015). The activation of TRPV4 was accomplished by various aspects of stimulating factors, including moderate heat (> 24 °C), osmotic pressure changes, cell swelling and chemical stimulation (Watanabe et al., 2003; Zhang et al., 2013a; Vergnolle, 2014). It was clearly indicated that TRPV4 was intimately associated with diverse physiological and pathological changes, such as skeletal dysplasia (Rock et al., 2008), tumors (Thoppil et al., 2015) and cardiovascular diseases (Randhawa and Jaggi, 2015). Importantly, an emerging role of TPRV4 in fibrosis was elucidated recently, which may help us develop novel therapeutic approaches for fibrosis (Adapala et al., 2013).

Fibrosis is a kind of chronic disease which was characterized by the formation of excessive accumulation of myofibroblasts secreted extracellular matrix (ECM) components in tissues and organs, especially alpha smooth muscle actin (α-SMA) collagen and fibronectin (Lopez-de la Mora et al., 2015). Generally, fibrosis is an adaptive event that contributes to the healing of injury in the short term. However, excessive fibrosis eventually occurs as a final outcome of organ dysfunction or failure (Wynn and Ramalingam, 2012). Inflammation is known to be a prelude to fibrosis (Hams et al., 2015). The mechanism underlying inflammation contributes to fibrosis is involved in fibroblasts activation, proliferation and differentiation into myofibroblasts (Albeiroti et al., 2015). Fibroblasts can be activated by a multitude of inflammatory mediators, including transforming growth factor beta (TGF-β) which is the major profibrotic cytokine, tumor necrosis factor-alpha (TNF-α), platelet-derived growth factor (PDGF), interleukin, and inflammatory mediators-mediated signaling pathways, including SMAD, Rho/ROCK, ERK and PI3K/AKT signaling pathways (Fang et al., 2013; Chen et al., 2014; Jiang et al., 2015; Kandhare et al., 2015). Till now, fibrosis was mainly found in heart (Fang et al., 2016), liver (Qin et al., 2016), lung (Oliver and Watson, 2016a; Qin et al., 2016), kidney

Abbreviations: α-SMA, α-smooth muscle actin; aa, amino acids; AHF, alcohol/high fat diet; AIP4, atrophin-interacting protein 4; ANK, ankyrin; ARS-L, arachidonate-like recognition sequence; ASL, airway surface liquid; BKCa, Ca^{2+}-dependent K^+; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; CaM, calmodulin binding domain; CFTR, cystic fibrosis transmembrane conductance regulator; CMT2C, charcot-marie-tooth disease type 2C; ECM, extracellular matrix; ER, endoplasmic reticulum; HEK, human embryonic kidney; HIF-1α, hypoxia inducing factor-1α; IP3R, inositol 1, 4, 5-trisphosphate receptor; IPF, idiopathic pulmonary fibrosis; MAP7, microtubule-associated protein 7; OMD, oligomerization domain; OTRPC4, osmosensitive transient receptor potential channel 4; PDZ-L, PDZ-like domain; PIBS, phosphoinositide-binding site; PKA, protein kinaseA; PKC, protein kinase C; PRD, proline-rich domain; RVD, regulatory volume decrease; SFKs, Src family tyrosine kinases; SGK1, glucocorticoid-induced protein kinase 1; SH3, SRC homology 3; siRNA, short interference RNA; SPSMA, scapuloperoneal spinal muscular atrophy; SRF, serum responsive factor; TGF-β1, transforming growth factor-beta 1; TRP, transient receptor potential; TRPA, transient receptor potential ankyrin; TRPC, transient receptor potential canonical; TRPM, transient receptor potential melastatin; TRPML, transient receptor potential mucolipin; TRPP, transient receptor potential polycystin; TRPV, transient receptor potential vanilloid; VR-OAC, vanilloid receptor-related osmotically activated channel; VRL2, vanilloid receptor-like 2; WNK, with no lysine

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https://doi.org/10.1016/j.gene.2017.10.067
Received 6 September 2017; Accepted 23 October 2017
Available online 07 November 2017
0378-1119/

(Zhou and Liu, 2016). Unfortunately, the precise pathogenesis of fibrosis is unclear and there are still no effective therapeutic strategies to cure fibrosis.

In recent years, a growing body of studies revealed a close connection between TRPV4 and fibrosis (Fernandez-Fernandez et al., 2008; Adapala et al., 2013; Song et al., 2014). For example, the activation of TRPV4 was demonstrated to be positive with the differentiation of cardiac fibroblasts into myofibroblasts in rat cardiac fibroblasts (Adapala et al., 2013). It was indicated that the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which was a product of the *CF* gene required for the activation of TRPV4 (Fernandez-Fernandez et al., 2008). Recently, we found over-expression of miR-203 prevented hepatic fibrosis by inhibiting TRPV4 expression (Song et al., 2014). Nevertheless, the fundamental mechanism underlying TRPV4 in fibrosis remains unclear. In this review, we try to collect the knowledge of TRPV4 and explore the mechanism between TRPV4 and fibrosis, further talk about whether regulating TRPV4 activity could provide a new therapeutic approach to fibrosis.

2. Overview of TRPV4

TRPV4, also termed osmosensitive transient receptor potential channel 4 (OTRPC4), vanilloid receptor-related osmotically activated channel (VR-OAC), vanilloid receptor-like 2 (VRL2), or TRP12, which was one of submit of TRPV family and first described in 2000 (Liedtke et al., 2000). TRPV4 is a non-selective cationic channel with high permeability to Ca^{2+} (Voets et al., 2002). It has been valuated that TRPV4 is widely expressed in heart, brain, lung, arteries, kidney, liver, skin, bone, urinary bladder, intestine, pancreas, ovary (Ferrandiz-Huertas et al., 2014). Nowadays, the physiological functions of TRPV4 was proposed which contain osmoregulation (Liedtke et al., 2000), mechanotransduction (Everaerts et al., 2010), thermoregulation (Sokabe and Tominaga, 2010), cell migration (Martin et al., 2012) and neuroinflammation (Boychuk et al., 2013). Up to present, it has firmly recognized that the activation of TRPV4 can be caused by osmotic changes, heat, mechanical and chemicals stimuli (Nilius and Flockerzi, 2014). Also, more and more agonists and antagonists of TRPV4 was explored in recent years (Table 1) (Liedtke et al., 2000; Watanabe et al., 2002; Suzuki et al., 2003b; Watanabe et al., 2003; Nilius et al., 2004; Kohler et al., 2006; Smith et al., 2006; Stotz et al., 2008; Vincent et al., 2009; Everaerts et al., 2010; Adapala et al., 2011; Jin et al., 2011; Bang et al., 2012a; Bang et al., 2012b; Ma et al., 2012; Thorneloe et al., 2012; Garcia-Elias et al., 2013; Balakrishna et al., 2014; McAlexander et al., 2014; Ma et al., 2015). Interestingly, among which, RN1734 and RN1747 have overlapping functions at different concentration (Vincent et al., 2009).

2.1. The structure of TRPV4

The TRPV4 channel consists of 871 amino acids (aa) with an N- and C-terminal intracellular tails which contain six transmembrane domains (TM1-6). Between the TM5 and TM6, the cation conductivity pore was clearly uncovered, which influences cation selectivity, especially Ca^{2+} (Voets et al., 2002). In the N-terminal tail, TRPV4 have a very short phosphoinositide-binding site (PIBS, aa121-aa125), which is proved to contribute to the activation of TRPV4 by physiological and chemical stimuli, such as arachidonic acid metabolites and epoxyeicosatrienoic acids (Garcia-Elias et al., 2013). Moreover, another important domain, the proline-rich domain (PRD, aa132-aa144) was found in the N-terminal tail of TRPV4 (D'Hoedt et al., 2008), while the PRD seem to tend to be involved in physical stimuli during the process of TRPV4 activation (D'Hoedt et al., 2008). Additionally, the N-terminal tail of TRPV4 comprised an arachidonate-like recognition sequence (ARS-L, aa402-aa408) which is also involved in TRPV4 activation (Nilius et al., 2003). Remarkably, the N-terminal tail of TRPV4 containing six ankyrin repeats (ANK1-6), each two neighboring ANKs exist antiparallel helices which formed five 'finger' loops, these finger loops were revealed to be intimately associated protein-protein interaction (Li et al., 2006). In addition, the ANKs have been shown to be very close to TRPV4 activity and participated the TRPV4 oligomerization, some of which are directly involved in the development of diseases (Li et al., 2006; Lamande et al., 2011). In the C-terminal tail, a calmodulin binding domain (CaM, 812aa-831aa) was illustrated that is also a protein- protein interactions region and the inositol 1, 4, 5-trisphosphate receptor (IP3R) is the most common interaction protein (Garcia-Elias et al., 2008). Besides, an oligomerization domain (OMD, 828aa-844aa) which is responsible for TRPV4 plasma membrane location, a PDZ-like domain (PDZ-L, last four aa) which is a protein interaction domain, and a TRP box were also

Table 1
Activation and inhibition of TRPV4.

Regulation	Category	Example	References
Activation	Fluid viscosity	High viscous loading	Garcia-Elias et al., 2013
	Mechanical force	Shear stress	Kohler et al., 2006
	Moderate heat	24–38 °C	Watanabe et al., 2002
	Osmotic changes	Hypotonic	Liedtke et al., 2000
	PH	Low PH	Suzuki et al., 2003b
	Endogenous ligands	5′, 6′-epoxyeicosatrienoic acid	Watanabe et al., 2003
		Acetylcholine	Adapala et al., 2011
		Dimethylallyl pyrophosphate	Bang et al., 2012a
		Endocannabinoid anandamide	Watanabe et al., 2003
	Plant-derived	Apigenin	Ma et al., 2012
		Bisandrographolide A	Smith et al., 2006
		Citrate	Suzuki et al., 2003b
	Synthetic ligand	4-alpha-phorbol 12, 13-didecanoate	Liedtke et al., 2000
		GSK1016790A	Jin et al., 2011
		RN1734, RN1747	Vincent et al., 2009
Inhibition	Specific inhibitor	AB159908	Adapala et al., 2013
		Butamben	Bang et al., 2012b
		Citral	Stotz et al., 2008
		HC067047	Everaerts et al., 2010
		GSK2193874	Thorneloe et al., 2012
		GSK2220691, GSK2337429A	Balakrishna et al., 2014
		GSK2334775	McAlexander et al., 2014
		RN1734, RN1747	Vincent et al., 2009
	Non-specific inhibitor	Gadolinium, lanthanum, ruthenium red	Nilius et al., 2004
		Nicotinic acid	Ma et al., 2015