TRPV4 CHANNEL REGULATES SKIN FIBROSIS AND IS ASSOCIATED WITH SCLERODERMA

Scleroderma or systemic sclerosis (SSc) is a multisystem idiopathic connective tissue disease with high morbidity and mortality. SSc is characterized by immune, inflammatory, vascular, and fibrotic manifestation in numerous organs including skin and lung. There are no effective medical treatments available and the exact cause remains poorly understood for SSc. Fibroblast differentiation into myofibroblast is a critical process in SSc and other fibrotic diseases. Emerging data support a role for both a mechanical signal, e.g., matrix stiffness, and a biochemical signal, e.g., transforming growth factor (TGF) beta1, in fibroblast activation, migration, and differentiation. Published work by our group and others showed that TRPV4, an ion channel in the transient receptor potential vanilloid family, a known mechanosensor, is activated by a range of mechanical and biochemical stimuli. We have obtained evidence that: i) increased numbers of TRPV4 positive myofibroblasts are present in dermal tissues of patients with SSc compared to healthy controls ii) TRPV4 deletion in mice prevented skin fibrosis development as assessed by dermal thickness, subcutaneous fat deposition, macrophage accumulation, myofibroblast abundance, and collagen deposition in skin in a bleomycin model of SSc iii) genetic ablation or pharmacologic antagonism of TRPV4 abrogates both matrix stiffness and TGFbeta1-induced dermal fibroblast differentiation and iv) TRPV4 regulates pro-fibrotic TGFbeta1 actions in a Smad-independent but PI3K-AKT-dependent manner. Altogether, these results, showed that TRPV4 calcium-permeable channel mediates fibrogenesis in SSc. Successful manipulation of the TRPV4 activity may be a targeted therapeutic approach to the treatment of SSc and other fibrotic diseases.

Biography

Shaik O Rahaman is an Assistant Professor at the University of Maryland, USA. His laboratory is interested in elucidating the signaling events underlying the pathogenesis of atherosclerosis and fibrosis. Dr. Rahaman earned his PhD in Molecular Biology at Jadavpur University, and a BS in Human Physiology (Honors), and an MS in Biophysics and Molecular Biology from University of Calcutta. From 2000-2014, Dr. Rahaman worked at Cleveland Clinic, Cleveland, USA, as a Postdoctoral Fellow, eventually as a Project Scientist and Assistant Professor. In 2013, he was the recipient of the American Heart Association Scientist Development Grant. Dr. Rahaman is the author or co-author of 21 research papers in high impact international peer-reviewed journals of repute. Dr. Rahaman has given numerous invited talks nationally and internationally, and is a reviewer/editorial board member in numerous scientific journals. Dr. Rahaman also served as a reviewer for National Institute of Health (USA).

srahaman@umd.edu