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TMEM 143 gene function characterization-possible role in glucose hemostasis

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TMEM-143 (Transmembrane protein 143) human gene is located in the Chr19q13.33 chromosomal region, which is known to be associated with risk of type-2 diabetes and cancer. TMEM-143 gene is translated into a protein of unknown function, predicted to contain a mitochondrial signal sequence and to reside as an integral membrane protein (dual-pass protein) in the mitochondria. In this study, we sought to elucidate TMEM-143 expression pattern, sub-cellular localization, and function. Screening of normal human tissues by RT-PCR revealed a high expression of TMEM-143 gene in metabolic tissues such as skeletal muscle tissue. RT-PCR and western blot revealed that undifferentiated C2C12 (myoblasts) and 3T3-L1 (pre-adipocytes) exhibited a differential expression profile of TMEM-143 during the process of differentiation into myotubes and adipocytes respectively. RT-PCR and Western blot analyses showed that potential or commonly used drugs for metabolic disorders modulated the expression level of TMEM-143. In these undifferentiated (differentiated) cell models, Rosiglitazone induced 2.2 (± 0.4)- and 2.6 (± 0.4)-fold increases in TMEM-143 mRNA and protein levels, respectively. Similarly, AICAR and Metformin upregulated TMEM-143 mRNA and protein levels by 2.0 (± 0.35)- and 2.5 (± 0.42)-fold respectively in these cellular models. In myoblasts and myotubes, insulin and BGP-15 increased TMEM-143 protein level by about 2-fold. 2D- and 3D-confocal fluorescence imaging (CFI) of TMEM-143 demonstrated a broad subcellular distribution of this protein with a predominant localization to mitochondria (Manders Overlap Coefficient, MOC: 0.5 ± 0.03 in myotubes vs. 0.3 ± 0.02 in adipocytes) and plasma membrane (MOC: 0.4 ± 0.01 in myotubes vs. 0.3 ± 0.02 in adipocytes). Nevertheless, this mitochondrial protein also exhibited a nuclear localization (MOC: 0.2 ± 0.01 in myotubes vs. 0.33 ± 0.02 in adipocytes) that was further confirmed by overexpressing TMEM-143 coupled to GFP in HEK293 cells, which do not express endogenously this protein. Moreover, 2D- and 3D-CFI uncovered significant cell (i.e. adipocytes, myotubes) size increase and changes in intracellular distribution (trafficking) of TMEM-143, induced by the pharmacological agents that affected its expression. Importantly, TMEM-143 strongly co-localized with glucose transporter type 4 (GLUT-4) (MOC: 0.75 ± 0.02). Silencing TMEM-143 with siRNA technology did not induce cell death and did not affect mitochondria biogenesis or membrane potential. However, TMEM-143 silencing induced a 2-fold decrease in GLUT-4 mRNA and protein levels, and a 2.4-fold decrease in pAKT protein level in insulin-stimulated C2C12 cells; subsequently, a significant reduction (by more than 50%) in glucose uptake was measured in both 3T3-L1 and C2C12 cells. These results indicate that TMEM-143 may play a physiological role in glucose homeostasis and merits further investigation.

Biography

Fouad Azizi has earned his PhD in Biophysical Chemistry at the Center of Molecular Biophysics, National Center for Scientific Research (C.N.R.S.), Orleans, France. He has a research track of over 20 years working in the USA. Currently, he is a Research Scientist, Director of electrophysiology laboratory and Manager of confocal imaging core in the Translational Research Institute, Academic Health System, Hamad Medical Corporation (HMC), Doha, Qatar. His research interests are focused in cancer and metabolic disorders.

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