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Evaluation of cationic channel TRPV2 as a novel biomarker and therapeutic target in leukemia-implications concerning the resolution of pulmonary dysfunction

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Patients treated during advanced and aggressive stages of leukemia face the risk of complications including pulmonary dysfunction and toxicity due to chemotherapy radiotherapy, and infiltration of leukemic blast cells (LBCs) into the lungs. Therefore, there is an urgent need for alternative or adjuvant therapeutic strategies. In this study, we sought to identify a molecular component of LBCs that, clinically, would serve as a reliable biomarker and can be exploited as a therapeutic target for hard to treat leukemia. The transient receptor potential vanilloid channel type 2 (TRPV2) exhibits oncogenic activity and plays a crucial role in immune inflammatory processes. Here, we found that TRPV2 mRNA levels were significantly higher in LBCs compared to normal human peripheral blood mononuclear cells (PBMCs). Alternative mRNA splicing was evidenced by upregulation of TRPV2 full length isoform ($TRPV2_{[97kDa]}$) and downregulation of its short pore-less isoform ($TRPV2_{[72kDa]}$) in LBCs. However, the opposite was found in PBMCs. Pharmacological modulation of TRPV2 by tranilast and SKF96365 inhibited LBCs proliferation through caspase-mediated apoptosis/cell cycle arrest, and involved the mitogen-activated protein (MAP) kinase pathways: extracellular signal-regulated kinases (ERKs), and the p38 group of protein kinases. Both drugs, in a dose-dependent manner, decreased and increased levels of $TRPV2_{[97kDa]}$ and $TRPV2_{[72kDa]}$ respectively, and downregulated the expression of pathogenic surface markers CD33 and CD38 in LBCs. TRPV2 siRNA mimicked tranilast and SKF96365 antiproliferative effects by triggering apoptosis/cell cycle arrest. Therefore, TRPV2 is a pharmacodynamic biomarker with pathogenesis relevance that can be targeted by anti-inflammatory drugs, and merits further exploration for potential clinical use.

Biography

Fouad Azizi earned his PhD in Biophysical Chemistry at the Center of Molecular Biophysics, National Center for Scientific Research, Orleans, France. He has a research track of over 20 years working in US universities on projects related to pulmonary diseases and blood disorders. He has published more than 12 papers in reputed journals and presented more than 15 abstracts at prestigious national and international conferences. Currently, he is a Research Scientist, Director of Electrophysiology Laboratory and Manager of Confocal Imaging Core at iTRI-HMC. His research interests are focused in the translational research of hematological cancers and pulmonary diseases.

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