Ecto-enzymes in interactions of vascular endothelium with blood circulating cells in physiology, pathology and therapy; could cells exchange their ecto-enzymes?

Abstract for general public

Research project objectives/Research hypothesis

Ecto-enzymes are proteins located in the cell membrane that actively metabolize molecules by which cells communicate with each other in physiology and pathology. They are found in significant amounts on blood cells and endothelium, a single layer of cells that cover the inside of blood vessels. Despite enzymatic activities, ecto-enzymes are able to interact with other cell surface proteins that can be particularly important in direct contact between cells. Such interactions between endothelium and blood cells or cancer cells enhance an unfavorable phenotype that promotes cardiovascular pathologies, cancer progression, and spreading. Previously, we contributed to understanding the role of ecto-enzyme activities that degrade signaling molecules, especially ecto-adenosine deaminase (eADA), in cardiovascular pathologies and cancer. The aim of this project is to investigate the changes of ecto-enzyme activities caused by the interactions of vascular endothelium with blood circulating cells, which could have a profound impact on the development of adverse phenotype of endothelial cells. Furthermore, we will focus on ecto-enzyme properties as adhesion molecules and investigate several related therapeutic possibilities in vascular pathologies and cancer.

Research project methodology

The effects of cell-to-cell interactions on the presence and activity of ecto-enzymes will be investigated in co-culture models of endothelial cells with blood circulating cells under static and flow conditions. The analyses will be performed using liquid chromatography (LC), LC coupled to mass spectrometry and live cell fluorescence microscopy. To analyze the potential of intercellular exchange of ecto-enzymes, we will identify which blood circulating cells are possible ecto-enzyme donors and how effectively endothelium function as ecto-enzyme acceptor. Non-enzymatic properties of ecto-enzymes, especially their actions as adhesion molecules and the mechanisms of their anchoring to endothelial cells will be studied in above co-cultures models and analyzed by live cell microscopy and bioluminescence resonance energy transfer. The process of intercellular ecto-enzyme exchange between blood cells and vascular endothelium will be also studied in mouse models of vascular inflammation and cancer by tracking labeled proteins derived from specific type of donor cells. Furthermore, therapeutic potential of ecto-enzyme activity and binding inhibitors will be evaluated. In particular, the compounds showing high efficiency in suppressing eADA catalytic activity and binding properties will be studied. Firstly, we will investigate their effects on stimulated endothelial cells and their interactions with blood circulating cells and then the most promising compounds will be analyzed to endothelial-protective properties in mouse model of atherosclerosis.

Expected impact of the research project on the development of science

This project focuses on a better understanding of the role of ecto-enzymes in endothelial physiology and pathology. In particular, it will explain the impact of cell-to-cell interactions on endothelial ecto-enzyme activities and signaling processes, which are dependent on their catalytic properties. Moreover, the results obtained will show whether ecto-enzymes act as adhesion proteins mediating such processes as cell adhesion and transmigration through endothelial layer. The project will provide new therapeutic targets for abnormal interactions with endothelial cells that play a pivotal role in cardiovascular pathologies and cancer progression. Potential impact of the project in the future includes pre-clinical evaluation of endothelial-protective compounds that can be successfully implemented in clinical trials as isolated therapies or increse the potential of already used drugs. Furthermore, the improved knowledge and validated methodologies/ technologies will be also applicable to study and treatment of other pathologies that based on alterations in cell-to-cell interactions.