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Role of the alpha 2 beta 1 integrin in leukemia chemoresistance

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This lecture will address a novel pathway involved in leukemia chemoresistance. Previous studies have identified alpha4beta1 integrin, which binds to the extracellular matrix fibronectin, as a major pathway in cell adhesion-mediated drug resistance of myeloma, B cell and myeloid leukemia. However, the integrin pathways promoting chemoresistance in acute T cell lymphoblastic leukemia (T-ALL) were not defined. Our recent findings showed that the collagen-binding integrin alpha2beta1 promoted the resistance of T-ALL cells to drug-induced apoptosis and enhanced clonogenic growth. This occurred via activation of the MAPK/ERK pathway, which upregulated the antiapoptotic protein Mcl-1 and the Mutidrug Resistance-associated Protein-1 (MRP-1). In addition, we found that alpha2beta1 signaling is implicated in the chemoresistance of leukemic T cell blasts from T-ALL patients. However, fibronectin, which binds to alpha4 and alpha5beta1 integrins had no effect. The role of alpha2beta1 integrin in chemoresistance is also seen in myeloid leukemia. Together these studies identified alpha2beta1 integrin as new pathway in cell adhesion-mediated drug resistance and suggest that leukemic cells in contact with collagen, which is an abundant matrix protein in the bone marrow, could escape chemotherapy and lead to the appearance of drugresistant cells. The clinical importance of alpha2 vs. alpha4 integrin in chemoresistance will be discussed.

Biography

Fawzi Aoudjit is a Professor in the Department of Microbiology-Immunology; Faculty of Medicine at Laval University (Québec, Canada). He attended Laval University in Quebec, where he received a PhD in Molecular Endocrinology and Physiology (1996). He completed Post-doctoral fellowships at the Institute Armand-Frappier in Montreal and at the Sanford-Burnham Research Institute in La Jolla California, after which he was appointed as an Assistant Professor at Laval University in Quebec (2001). His research interests focus on the functional role of integrin-extracellular matrix interactions in the regulation of normal and malignant cells, with a focus on T cells. His previous studies have been central in understanding how integrins regulate anoikis and death-receptor-mediated apoptosis. He is now a full Professor at Laval University and his current research focuses on how extracellular matrix regulates the chemoresistance and dissemination of leukemia, and the development of autoimmune diseases.

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