INTEGRIN SELECTIVE LIGANDS MODULATING LEUKOCYTE ACTIVATION, MIGRATION AND DEATH

Christina Barja-Fidalgo
Laboratory of Biochemical & Cellular Pharmacology- IBRAG, UERJ

Neutrophils adhere on vascular endothelium and directly migrate toward inflamed tissue to exert their primary defense function. Integrin are receptors that drive cell adhesion and motility and interfere with cell activation, functions and survival. Acting as both anchoring molecules and signaling receptor, transducing signals outside-in and inside-out, integrins are potential targets for therapeutic and diagnostic opportunities. Disintegrins are a family of cystein-rich low-molecular weight peptides that usually contain an RGD sequence, a cell attachment site of ECM and cell surface proteins recognized by integrins. They are considered selective and competitive antagonists of integrins, being potent inhibitors of platelet aggregation and cell-cell/cell-ECM interactions. We reported that RGD-disintegrins, selectively interact with integrin ($\alpha M\beta 2$; $\alpha 5\beta 1\alpha v\delta/o\rho$ $\alpha\varpi\beta 3$) on human neutrophils, interfering with cell functions through the activation of integrin-coupled intracellular signaling pathways. Recently showed that, a selective ligand of $\alpha 9/\alpha 4\beta 1$ integrin, VLO5, induces neutrophil chemotaxis, cytoskeleton mobilization and potently inhibiting neutrophil spontaneous apoptosis. These effects are mediated VLO5 interaction with $\alpha 9\beta 1$ integrin, activating the focal adhesion cascade. VLO5 effects on the delay of neutrophil is modulated by PI3K, ERK-2 MAPK and NFκB pathways that seems to interfere with the balance between anti- and pro-apoptotic Bcl-2 family members and with mitochondrial membrane potential. Data emphasize mechanistic details of the role of $\alpha 9\beta 1$ integrins interactions on human neutrophils and support the use of disintegrins as prototypes to develop logical combinations of drugs to optimize or minimize the susceptibility of a selected target cell population to apoptosis during therapeutic interventions. (FAPERJ, CNPq, IFS-Sweeden)