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Integrin inhibition in the tumor microenvironment

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Tumor cell migration and invasion are critical steps in the metastatic cascade and depend on the interaction between tumor cells, the extracellular matrix (ECM) and the endothelial cells. Integrins are key receptors that link cells and ECM, acting as mechanical sensors of the cell microenvironment. Particularly, Arg-Gly-Asp (RGD)-binding integrins such as the v 3 and 5 1 integrins are of special interest in cancer progression since several well-known cancer oncogenes were identified as crucial regulators of integrin traffic and, therefore, of cell invasion and metastasis. Integrins also interact with growth factor receptors resulting in an important cross talking between intracellular signaling pathways triggered by ECM components and growth factors. Recent studies have provided evidence of distinct roles for v 3 and 5 1 integrins in the migration process, where 5 1 integrin clustering supports high matrix forces while v 3 integrin starts mechanotransduction. Therefore, v 3 and 5 1 integrins became an attractive target for pharmacological inhibition in cancer therapy and metastasis prevention. Cilengitide, the first integrin inhibitor based on the RGD motif, is currently under clinical trials in cancer patients with limited success. Efforts to achieve a better understanding of the integrin roles in cancer progression and searches for better inhibitor candidates are needed. We have used a recombinant RGD disintegrin from the Brazilian snake *Bothrops alternatus* to study the effects of v 3 integrin inhibitions. This protein impairs αvβ3/VEGFR2 cross talking, inhibits HUVEC proliferation, decreases migration speed, directionality and changed the migration mode of a highly invasive tumor cell line from single to collective cell migration. Our data suggest that RGD-disintegrins are interesting as lead compounds for v 3 integrin inhibition.

Biography

Heloisa Sobreiro Selistre de Araujo has completed her PhD from São Paulo University in Brazil and Post-doctoral studies from Oklahoma State University, USA. She is a Full Professor of Biochemistry and Molecular Biology at Federal University of São Carlos, Brazil. She has published more than 120 papers in reputed journals and has been serving as an Editorial Board Member of several journals.

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