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Transcriptional factor Snail and MMP-9 signaling axis controls tumor neovascularization, growth and metastasis in mouse model of human ovarian carcinoma

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Snail, a transcriptional factor and repressor of E-cadherin is well known for its role in cellular invasion. It can regulate epithelial to mesenchymal transition (EMT) during embryonic development and in epithelial cells. Snail also mediates tumor progression and metastases. Silencing of Snail and its associate member Slug in human A2780 ovarian epithelial carcinoma cell line was investigated to identify its role in tumor neovascularization. Live cell sialidase, WST-1 and immunohistochemistry assays were used to evaluate sialidase activity, cell survival and the expression levels of tumor E-, N- and VE-cadherins, and host endothelial CD31+(PECAM-1) cells in archived paraffin-embedded ovarian A2780, A2780 Snail shRNA GIPZ lentiviral knockdown (KD) and A2780 SlugKD tumors grown in RAGxCγ double mutant mice. Oseltamivir phosphate (OP), anti-Neu1 antibodies and MMP-9 specific inhibitor blocked Neu1 activity associated with epidermal growth factor (EGF) stimulated A2780 ovarian epithelial carcinoma cells. Snail and Slug KD A2780 cells abrogated the Neu1 activity following EGF stimulation of the cells compared to A2780 cells. OP treatment of A2780 and cisplatin-resistant A2780cis cells reproducibly and dose-dependently abated the cell viability with a LD50 of 7 and 4 μM, respectively. Heterotopic xenografts of A2780 ovarian tumors developed abnormally robust and bloody tumor vascularization in RAGxCγ double mutant mice. Preclinical in vivo anti-tumor activity of OP monotherapy at 50 mg/kg daily intraperitoneally did not significantly impede A2780 tumor growth rate in a time-to-progression but did cause a significant reduction of lung metastases compared with the untreated and OP 30 mg/kg cohorts. A2780 Snail KD cells, but not the Slug KD member completely abrogated the tumor vascularization, growth and spread to the lungs in these mice. A2780 and A2780 Slug KD xenograft tumors expressed high levels of human N- and VE-cadherins, and host CD31+ endothelial cells, while one A2780 Snail KD tumor expressed higher levels of E-cadherin and host CD31+ cells. OP 50mg/kg cohort tumors had reduced numbers of host CD31+ cells compared to those from the untreated control and OP 30mg/kg cohorts. These findings uncover a novel organizational signaling platform connecting the Snail-MMP-9 signaling axis in amplifying the Neu1 sialidase and MMP-9 cross-talk in regulating EGF receptors, tumor neovascularization, growth and invasiveness.

Biography

Myron R Szewczuk received his PhD (Biology and Immunochemistry) from the University of Windsor, Windsor Ontario in 1974 and completed his postdoctoral studies in Cellular Immunologyunder Dr. Gregory W.Siskind at Cornell University Medical College, New York City, in 1978. From 1978-81, Dr. Szewczuk was an Assistant Professor of Pathology at McMaster University, Hamilton, Ontario. In 1981, he joined the Dept. of Microbiology & Immunology (now Biomedical and Molecular Sciences) as an Associate Professor of Immunology at Queen's University, Kingston, Ontario. In 1986, he received tenure and became full Professor of Immunology and Associate Professor of Medicine. He is presently a full time faculty member at Queen's University with an active teaching and research program in immunology and cancer. He has published over 100 papers, chapters and reviews primarily in the field of immunology and cancer.

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