

Expression of the p53 target SERPINE1 (PAI-1) gene is required for human tumor cell migration upon plastic conversion to a stem cell-like phenotype in response to TGF- β 1+EGF

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The emergence of highly aggressive, cancer stem cell-like, subtypes of human squamous cell carcinoma (SCC) reflects increased transforming growth factor- β 1 (TGF- β 1) synthesis and epidermal growth factor receptor (EGFR) amplification. Cooperative TGF- β /EGFR signaling promotes cell migration and induces expression/activation of proteases (e.g., plasminogen, MMPs) and protease inhibitors that regulate stromal remodeling resulting in the acquisition of an invasive phenotype. Paradoxically, plasminogen activator inhibitor type-1 (SERPINE1, PAI-1), the major inhibitor of plasmin generation, is also upregulated under these conditions and is an early event in tumor progression. Increased PAI-1 expression temporally and spatially modulates plasmin-initiated pericellular proteolysis, preserving a stromal scaffold permissive that facilitates invasive potential. Combined TGF- β 1+EGF treatment was used to investigate mechanisms underlying induced epithelial-to-mesenchymal transition (EMT) in *ras*-transformed human keratinocytes. Dual stimulation with TGF- β 1+EGF resulted in keratinocyte "plasticity" and pronounced colony dispersal. Transcriptome analyses indicated that cells undergoing EMT expressed high β 1 integrin levels and possessed stem cell-like characteristics. The most up-regulated transcript encoded PAI-1, an established marker of aggressive carcinoma cells and a functional promoter of cell migration suggesting that PAI-1 plays a critical role in epithelial stem cell biology. PAI-1 knockdown alone effectively inhibited TGF- β 1+EGF-dependent cell scattering, indicating a functional role for this SERPIN in the dual-growth factor model of induced motility. Identification of signaling networks and their effect on specific invasion-promoting target genes, such as PAI-1, may lead to the development of pathway-specific therapeutics that impact late-stage events in human cutaneous epithelial tumor progression. Supported by grants from the NIH (GM57242) and the NYSDOH Empire State Stem Cell Trust Fund (C024312).

Biography

Dr. Paul J. Higgins received his Ph.D. in molecular biology from New York University. He was a post-doctoral fellow and Assistant Member at the Memorial Sloan-Kettering Cancer Center before assuming the Directorship of the Center for Cell Biology & Cancer Research at Albany Medical College. Dr. Higgins has published more than 250 papers, served on a number of NIH and international review panels and is an Editor of various biomedical journals. He was the recipient of the University of Florida College of Medicine Excellence Award in Molecular Medicine in 2008.