Tumor-stroma interaction: Mechanism of transdifferentiation of stromal cells and its modulation

Peter Brenneisen

Heinrich-Heine-University Düsseldorf, Medical Faculty, Institute of Biochemistry & Molecular Biology I, Universitätsstr. 1, Geb. 22.04

D-40225 Düsseldorf, Germany

Tel: +49-211-81-12715

Fax: +49-211-81-13029

E-mail: Peter.Brenneisen@uni-duesseldorf.de Peter.Brenneisen@web.de

Tumor progression is characterized by the local accumulation of extracellular matrix components and stromal cells surrounding the tumor cluster, a phenomenon called tumor-stroma interaction (Bhowmick and Moses 2005, Liotta and Kohn 2001). Disturbance in stroma, composed of inflammatory cells, small vessels, fibroblastic and myofibroblastic cells, constitutes the desmoplastic reaction, suggested to be essential in the development of the invasion process. In melanoma and carcinoma, a wide variety of different cytokines and growth factors are expressed by tumor cells and stromal cells which via autocrine and/or paracrine effects promote neovascularization and tumor growth as well as migration during tumor invasion (de Wever and Mareel 2003, Liotta and Kohn 2001). One of the cellular components of the stroma reaction is the tumor-associated fibroblast, a modulated fibroblast called myofibroblast which has acquired the capacity to express α-smooth muscle actin (αSMA) by a process called transdifferentiation, and to synthesize important amounts extracellular matrix components (Kunz-Schughart and Knüchel 2002). Cancer cells and myofibroblasts exchange proteolytic enzymes, growth factors, and cytokines which promote proliferation and survival as well as invasion (de Wever and Mareel 2003). The molecular mechanisms underlying the transdifferentiation of stromal cells as well as the tumor invasion-promoting effect of myofibroblasts have not been fully elucidated at present. Recently, we showed a paracrine effect of tumor cell-derived transforming growth factor beta 1 (TGFβ1) on downregulation of gap junctional intercellular communication between stromal fibroblasts, dependent on generation of reactive oxygen species (ROS). Precinubation of stromal cells with selenite counteracted the ROS-mediated downregulation of the homologous intercellular communication of these fibroblasts (Stuhlmann et al. 2003, 2004). Novel findings from our lab deal with the involvement of ROS in molecular processes of transdifferentiation (Cat et al. 2006, Cat and Brenneisen 2009, Allili et al. 2014). In that context, a novel concept of protection of stromal cells against the dominating influence of tumor cells in tumor-stroma interaction by antioxidants or micronutrients may reflect an initial approach for new therapeutic strategies in chemoprevention of tumor invasion (stromal therapy) (Fig. 1). Recently, the importance of (myo)fibroblasts in tumor-stroma interaction was corroborated by the finding that tumor cells protect these cells from oxidative damage, reflecting stromal resistance (Werth et al. 2008). The understanding of the cellular interaction between tumor and stroma cells could assist in the development of novel therapeutic strategies to combat metastatic spread more efficiently in the future. In that context, dextran-based cerium oxide nanoparticles seem to be a promising tool in prevention of tumor invasion (Allili et al. 2011).

References


Fig. 1 Chemoprevention of tumor progression. Tumor cells release growth factors/cytokines, which initiate ROS-dependent changes of gene expression in stromal cells resulting in proinvasive signals. Proinvasive signals stimulate invasive capacity of cancer cells. These signals are lowered or prevented by treatment of stromal cells with antioxidants and with cerium oxide-based nanoparticles (stromal therapy).

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