Exploration of Paracrine and Contact-Dependent Cell-Cell Signaling within the Tumor Microenvironment

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Summary: The effects of paracrine and contact-dependent signaling in the tumor microenvironment were explored using a reconfigurable silicon platform, which allows for spatial and temporal control of cell populations in culture.

The growth and behavior of a developing tumor are dependent upon complex pathways of intercellular communication within the tumor microenvironment. This communication involves both paracrine and contact-dependent signaling, but the identity and function of the specific intercellular interactions remain elusive. Traditional co-culture experiments are inadequate for proper study of these signaling interactions because effective spatial management of cell populations in co-culture is impossible. We have developed microfabricated platforms, known as micromechanical reconfigurable culture (MRC) [1], which facilitate precise and dynamic manipulation of cell populations in culture so that paracrine signaling and juxtacrine signaling effects can be studied independently. Cells of two distinct populations can be co-cultured such that they either contact one another (Fig 1.a bottom) or are separated by an 80-micron gap (Fig 1a. top). The co-cultured cell populations can subsequently be independently isolated with ease for further analysis. HT-1080 human fibrosarcoma tumor cells were co-cultured with normal human lung fibroblasts (NHLF) using conventional methods (conditioned media transfer, Transwell assay) as well as our MRC contact and gap co-culture modes. mRNA analysis was performed on each population using qPCR arrays (Qiagen) for genes involved in the control of angiogenesis, a critical process in tumor development. Preliminary results suggest that short-range secreted factors are important in signaling between tumor cells and their neighboring stroma. Additionally, our data support a specific role for direct cell-cell contact in the control of angiogenic processes.

Fig. 1. a) HT-1080 tumor cells and normal human lung fibroblasts (NHLF) co-cultured in gap mode (top) and contact mode (bottom) on MRC device. b) Relative mRNA expression of angiogenesis-associated genes in HT1080 and NHLF cells subject to various forms of co-culture involving long-range (media transfer, Transwell) or short-range (gap co-culture) paracrine signaling only, or contact-dependent signaling (contact co-culture). The monoculture control involved cells of the same type being cultured in contact co-culture mode.