REGULATION OF TISSUE FACTOR AND ANGIOGENESIS RELATED GENES BY CHANGES IN CELL SHAPE

Chloe C. Milsom and Janusz Rak*

Henderson Research Centre in affiliation with McMaster University
Henderson Research Centre, Rm 216, 711 Concession Street, Hamilton, Ontario
L8V 4C3 (jrak@thrombosis.hhscr.org)

INTRODUCTION. During development, tissue injury and cancer, epithelial cells engage in communication with the vascular system by using several molecular mediators acting directly or through changes in the haemostatic system (1; 2). The latter category is epitomized by the procoagulant cellular receptor known as tissue factor (TF).

RESULTS. Here we show that when cellular architecture is altered by a shift in culture conditions from monolayer to three-dimensional multicellular spheroids, expression of multiple angiogenesis effectors (VEGF, TSP-1, Ang-1 and TF) is profoundly altered. In particular, TF is dramatically upregulated in a transformed murine breast epithelial cell line (EMT6) under these conditions (see Figure 1).

This appears to be linked to a particular change in cell shape and cytoskeletal (actin) reorganization, as treatment of these cells with cytochalasin D (Cyt D), but not with latrunculin B (Lat B) recapitulates and potentiates TF upregulation. Collectively, these results suggest that the ability of epithelial cells to interact with the vascular system via expression of the TF gene (and other effectors) is under the control of complex alterations in cellular architecture (see Figure 2).
DISCUSSION. The evidence presented here suggests that perturbations in the state of the cellular cytoskeleton may play a significant role in the regulation of the angiogenic and procoagulant phenotype of epithelial cells. This complements and extends the previously recognized pro-angiogenic influence of hypoxia, inflammation, paracrine stimulation with growth factors and activation of oncogenic pathways (1;3;4). In particular, our study demonstrates that cells grown under several cytoskeleton and cell shape altering conditions (sparse, dense and spheroid cultures and in the presence or absence of Cyt D) respond to these changes by reprogramming their expression of several angiogenesis-related genes, including VEGF, TSP-1, TSP-2, Ang-1 and TF. These observations suggest that cytoskeleton-related signals may be among important and hitherto unappreciated mechanisms that control and coordinate the expression of the angiogenic phenotype in activated and/or transformed epithelial cells.

REFERENCES