

## Cathepsin D and Breast Cancer: mechanisms of action in tumor proliferation, angiogenesis, apoptosis and fibroblast invasive growth

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The lysosomal aspartic protease cathepsin D is over-expressed and hyper-secreted by epithelial breast cancer cells. This protease is an independent marker of poor prognosis in breast cancer being correlated with the incidence of clinical metastasis. We previously showed that over-expressed cathepsin D stimulates tumorigenicity, metastasis and plays an essential role in the multiple steps of tumor progression, in stimulating cancer cell proliferation, and angiogenesis, as well as in inhibiting tumor apoptosis. Moreover, we demonstrated that a mutated D231N cathepsin D devoid of catalytic activity still proved mitogenic for cancer and endothelial cells. As tumor epithelial-fibroblast cell interactions are important events in cancer progression, we recently investigated whether over-expressed cathepsin D might also affect fibroblast behavior. Indeed, we demonstrated a cathepsin D requirement for fibroblast invasive growth using a three-dimensional co-culture assay with cancer cells secreting or not pro-cathepsin D. Moreover, ectopic expression of cathepsin D into cathepsin D-deficient fibroblasts stimulated three-dimensional outgrowth. Outgrowth was associated with a significant increase in fibroblast proliferation, survival, motility and invasive capacity, as well as an activation of the *ras*-MAP kinase pathway. Interestingly, all these stimulatory effects on fibroblasts were independent of the cathepsin D proteolytic activity. Finally, pro-cathepsin D secreted by cancer cells was captured by fibroblasts and partially mimicked transfected cathepsin D effects. We concluded that cathepsin D is crucial for fibroblast invasive outgrowth and could act as a key paracrine communicator between cancer and stromal cells independently of its catalytic activity.

In summary, we propose that cathepsin D is a mitogen for both cancer, endothelial and fibroblast cells, by acting extracellularly as a cytokine and triggering either directly or indirectly an as yet unidentified cell surface receptor.