ImmunoTools IT-Box-Cy55M-Award 2013

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Modulation of gene expression and biological activity of breast cancer cells by stromal mesenchymal stem cells

Tumor progression is not only determined by the tumor cells themselves, but also by the microenvironment in which they are embedded. Stromal cells, such as carcinoma-associated fibroblasts, has long been known for their tumor-promoting activity. A new type of stromal cell, the mesenchymal stromal/stem cell (MSC), has recently received much attention. MSCs, whose major source is the bone marrow, are defined by their ability to differentiate to osteoblasts, chondroblasts and adipocytes, to adhere to plastic surfaces and to express certain surface molecules, CD105, CD73 and CD90, and to be deficient of CD45, CD34, CD14 and CD11 (Dominici et al., 2006).

A prominent feature of MSCs is their attraction to injuries where they facilitate wound healing (Brooke et al., 2007). By secreting similar cytokines as wounds, tumors chemoattract MSCs as well. As non-healing wounds, however, tumors fail to appropriately respond to MSCs and rather seem to "use" the MSC-derived cocktail of cytokines and growth factors to foster their expansion (Dittmer, 2010). We and others have found that MSCs have profound effects on breast cancer cells (BCCs) (Dittmer et al., 2009; Karnoub et al., 2007). These effects mostly lead to breast cancer progression (Dittmer et al., 2011). A number of soluble factors, such as CCL5, CCL2 and CXCL1, have already been identified to be involved in MSC/BCC interaction (Dwyer et al., 2007; Karnoub et al., 2007).

In order to further define the mechanisms by which MSCs interact with BCCs, we have performed gene expression profiling by microarray analysis. We found that the expression of a number of genes in BCCs is changes when they are co-cultured with MSCs at a ratio as low at 1 MSC/50 BCCs. By using transwell assays and MSC-derived conditioned media we were able to show that these gene-regulatory effects of MSCs on BCCs do not require direct cell-cell contact, but rather seem to be driven by paracrine mechanism(s). Experiments with kinase inhibitors suggest that cytokines and growth factors are involved in the communication between MSCs and BCCs. To explore which cytokines and growth factors are responsible we are planning to substitute MSC-derived conditioned medium by a single cytokine/growth factor or by a cocktail of cytokines/growth factors. For this task, we will need to test a large number of cytokines and growth factors. The ImmunoTools IT-Box Cy55M containing 55 specific cytokines/growth factors would be an ideal tool to exactly perform this task. Many of these factors have interspecies compatibility and could therefore be used for both human and mouse breast cancer cells.

References

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