

Beta blockers and their Control of (Ab) Normal Stem Cell Mobilization

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Many stem cell biology researchers have been trying to answer whether there are differences or similarities between the biology of Cancer Stem Cells (CSC), Hematopoietic Stem Cells (HSC) and Mesenchymal Stromal Cells (MSC) [1,2]. The translation of basic science discoveries into clinical practice has not been robust to date.

Recently Wang et al. [3] performed a retrospective analysis from 722 patients treated for Non-Small-Cell Lung Cancer (NSCLC) who received definitive radiation therapy at their institution. The analysis was done in order to elucidate a link between the use of beta-blockers and outcome in lung cancer. The potential authors have concluded that patients taking beta-blockers (n=155) had improved Distant Metastasis-Free Survival (DMFS; P<0.01), Disease Free Survival (DFS; P<0.01), and Overall Survival (OS; P=0.01), but not Locoregional Progression-Free Survival (LRPFS; P=0.33) compared with patients not taking beta-blockers (n=567). The lack of association between LRPFS suggests that beta-blockade may have an effect on metastatic process rather than a direct effect on the tumor [3].

There are correlations with observations of the interactions between normal HsC, MsC and stem cell mobilization process. The coordinated release of cytokines coupled with the adrenergic stimulation leads to proper stem cell maintenance and their egress from the bone marrow stroma. It has been described that sympathetic nerve signals are required for HSC mobilization [2]. The work by Frenette and colleagues showed that MSCs expressing nestin constituted an essential HSC niche [2,4]. Nestin+ MSCs express beta-3- adrenergic receptor. The CXCL12/SDF-1 is a critical chemokine for the migration of HSCs [4]. Blockade of CXCR4 is effective in induction of HSC mobilization [5]. The expression of Cxcl12 is under the influence of norepinephrine. In addition, osteoblasts in the bone marrow express beta-2-adrenergic receptor.

Given the prophylactic effect of beta-blockers on distant metastases in NSCLC, it is possible to hypothesize that the metastatic process in NSCLC (and perhaps other cancers too) are driven by egress of tumor cells from primary stroma [1] governed by local change in cytokines, chemokines, and adhesion molecules upon adrenergic stimulation. Lung cancer needs further therapeutic improvements and while many therapeutic modalities recently added to chemotherapy or radiation therapy provide modest clinical benefit, they are accompanied by significant and sometimes prohibitive side effects (i.e. anti-angiogenic therapies). The use of beta-blockers as therapeutic agents with anti-metastatic potential seems quite appealing and warrants further study and prospective validation.

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