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POSTER ABSTRACTS

501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

The Role of Hematopoietic Stem Cells in Lung Cancer Response to Radiation Therapy

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Non-small cell lung carcinoma (NSCLC) comprises approximately 85% of all lung cancer cases in the United States. We demonstrated that after radiation therapy (RT), bone marrow-derived hematopoietic stem and progenitor cells (HSPCs) are recruited to the NSCLC tumor microenvironment (TME). These HSPCs seemed to positively affect tumor regrowth as their numbers directly correlated with regrowth rates. The TME is comprised of tumor tissue, stromal cells, immune cells, bone marrow-derived cells, and extra cellular matrix (ECM) proteins and has emerged as one of the predominant defensive weapons with which cancer can resist various forms of therapeutic intervention. The ability of tumor-associated HSPCs to maintain hematopoietic potency in tumors suggested a prominent role of these cells in tumor physiology, however; what was missing was a mechanistic understanding of: 1) how HSPCs participate in tumor growth post-RT and 2) how HSPCs are maintained within tumors.
To answer these questions, we established NSCLC tumors in mice using Lewis Lung Carcinoma (LLC) cells and assessed tumor-associated HSPCs activity and molecular changes in the TME following RT. We observed that RT induces the TME to produce colony stimulating factor (CSF)-1, a factor that promotes the differentiation of HSPCs into tumor supportive M2-macrophages. Adoptive transplantation of dsRed labeled HSPCs into tumor bearing mice followed by RT directly showed the differentiation of HSPCs into M2-macrophages and a concomitant increase in the regrowth of tumors post-RT. Use of a therapeutic inhibitor of the CSF-1 receptor (GW2580) prevented HSPC differentiation in to M2-macrophages and significantly decreasing regrowth rates.
We next assessed how tumor-associated HSPCs maintain their hematopoietic potency within the TME. Analysis of tumors demonstrated high expression levels of the laminin 5-1-1 isoform, which is known to bind CD49f (integrin alpha 6), a marker of functional HSPCs. Tumors exposed to RT demonstrated significantly reduced expression of both laminin 5-1-1 and CD49f. When bound, CD49f inhibits phosphorylation of focal adhesion kinase (FAK) resulting in maintenance of pluripotent stem cells. Analysis of tumor-associated HSPCs demonstrated significantly higher levels of phosphorylated FAK following tumor exposure to RT. Since RT induces HSPC differentiation in to M2-macophages, this observation suggests that tumor-associated HSPC functionality is maintained through the interaction between laminin 5-1-1- and CD49f. The identification of single HSPCs that differentiated in to M2-macrophages and which expressed phosphorylated FAK supports this conclusion.
Taken together, this data province's evidence of a mechanism wherein RT disrupts laminin 5-1-1/CD49f interactions releasing tumor-associated HSPCs from maintenance signals. Concomitantly, RT induces the production of CSF-1 within the TME, which induces these "released" HSPCs to differentiate into tumor supportive M2-macrophages and promote tumor regrowth post-RT. Overall, these studies define a new understanding of tumor biology in which HSPCs are significant mediators of tumor response to RT. These findings also identify new cellular and molecular pathways to target in the treatment of NSCLC to achieve more optimal clinical outcomes.

Disclosures No relevant conflicts of interest to declare.

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