



Correlation between cancer stem cells (CSCs) and tumor-infiltrating lymphocytes (TILs): do TILs interact with CSCs in non-small cell lung cancer?

Min Ling, Xiaolong Yang

Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada

Correspondence to: Xiaolong Yang, Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada.

Email: yangx@queensu.ca.

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It has been well recognized that dynamic interaction between tumor cells and the immune system is critical for tumorigenesis (1,2). However, how cancer cells interact with immune cells during progression of clinical cancer patients is largely unknown. Recently, it has been shown that cancer stem cells (CSCs), which possess characteristic associated with normal stem cells, like self-renewal and differentiation (3), become more metastatic and drug resistant by interacting with the immune system in the microenvironment (4). On the other hand, it has also been reported that the presence of tumor-infiltrating lymphocytes (TILs), a type of immune cells, are positively associated with the prognosis and outcome of non-small cell lung cancer (NSCLC) (5,6). However, whether there is a correlation between TILs and CSCs in NSCLC patients is largely unknown.

In a recent paper published in *Ann of Transl Med*, Masciale *et al.* performed a correlation study between TILs and CSCs in NSCLC human surgical specimens from 12 patients (7). By utilizing ALDEFLUOR assays, aldehyde dehydrogenase (ALDH) activity was measured and served as a marker for CSCs. The levels of immune cell markers, CD3⁺, CD4⁺, or CD8⁺ TILs, were analyzed by fluorescence-activated cell sorting (FACS) analyses. Data analysis showed a moderate to high positive linear and rank correlation between ALDH-positive (ALDH⁺) CSCs and CD3⁺ or CD8⁺ TILs in NSCLC. However, there is no correlation between ALDH⁺ and CD4⁺ cells.

This is the first report studying the relationship between CSCs and specific subtypes of TILs in NSCLC. There are three types of TILs named cytotoxic T cell, helper T cell, and regulatory T cell (Treg) (8). CD3 is the surface marker of helper and cytotoxic T cells, whereas CD8⁺ T cells recognize antigen that is expressed on the surface of class I MHC molecules, and function mainly as cytotoxic T cells. CD4 is the surface marker of helper T and Treg cells. It is intriguing that this study finds a positive correlation between CSCs and CD3⁺/CD8⁺ cytotoxic and helper T TILs in NSCLC. Previous studies have demonstrated TILs correlate with reduced recurrence risk and improved disease-free survival (DFS) in NSCLC (5,9,10). Since CSCs are associated with poor survival in NSCLC (11,12), it is expected that CSCs should have negative correlation with TILs, which is in contrast with the findings obtained from this study. In addition, Huang *et al.* demonstrated no correlation was observed between CD8⁺ TILs and CD133, which is another CSCs marker, in 172 resected NSCLC samples (13). The inconsistency of these studies may be caused by different markers for CSCs (ALDH *vs.* CD133) and TILs subtypes (CD8⁺ *vs.* CD3⁺/CD4⁺/CD8⁺), and different stages of NSCLC samples (primary tumor *vs.* metastasis) used in these studies. In addition, only 12 NSCLC patient samples were used in this study, which may give insufficient statistical power. Given the biological variability of different subtypes of immune cell

infiltration both within primary tumors and among NSCLC metastases, more comprehensive analyses on multiple TILs subtypes using different stages of cancer development are warranted in larger cohort of patients.

Nonetheless, this study provides a novel research direction toward our understanding of correlation between CSCs and subtypes of TILs. Further elucidation of the molecular mechanism underlying this correlation in various types of cancer will provide critical information on how CSCs interact with tumor microenvironment in tumorigenesis and novel strategies in cancer immunotherapy in the future.

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Footnote

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