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Janus-faced Kupffer cells in tumor metastasis

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Kupffer cells are the resident liver macrophages of the liver; other tissues also have resident immune cells e.g., microglia in the brain.[1] These cells have a distinct embryonic lineage when compared with circulating myeloid cells. In both the liver and brain micro-environments activation of their resident immune cells results in the synthesis of multiple growth factors and cytokines which stimulate tumor growth and that in part provide the permissive "soil" in which the tumor "seed" grows.[2,3] In the manuscript by Wen et al., studies defined whether liver localized Kupffer cells supported or inhibited the growth of colorectal tumor metastases in an immune competent animal model.[4] The authors also determined whether the most important changes in the biology of metastatic tumors were associated with the numbers of CD3-positive T cells and the numbers of VEGF and iNOS expressing cells.[4]

Using chemical means, deletion of the Kupffer cells from the liver enhanced the number of colorectal metastatic lesions in the liver within 16 d. This effect could either be directly due to the initial Kupffer cell depopulation itself or more likely due to the repopulation of activated Kupffer cells back throughout the liver which began at day 3 and continued to completion by day 16. The situation regarding Kupffer cells was reversed in established tumors; in established tumors deletion of Kupffer cells at day 18, albeit at a very late stage of growth resulted in less tumor load within the liver; indeed the resultant loss of tumor burden comparing Kupffer cell deletion at day 14 to day 18 was striking. The loss of Kupffer cells at this late stage of tumor growth correlated with invasion of $CD3^+$ T cells into the tumor and increased iNOS levels, suggestive of an activated anti-tumor immune response. Studies by other groups have argued that tumor macrophage infiltration and T-cell infiltration into tumors is often associated with a favorable prognosis possibly as macrophages can stimulate T-regulatory cell invasion into tumors.[5-8]

The present studies also raise the question as to whether Kupffer cells can be considered as a therapeutic target in the treatment of liver cancer or in the development of metastatic colon cancer. Drugs such as cyclosporine A, NSAIDs, and drugs that modulate multiple sclerosis and arthritis could all be considered as immune cell modulators that could also act to dampen the function of activated Kupffer cells and the resultant expression of paracrine cytokines.[9] Because the model system used in the present studies involved a chemical rather than inducible genetic approach, the precise roles of Kupffer cell deletion and activated Kupffer cell repopulation in the initial growth of colorectal tumors cannot easily be separated, but negative data showing depletion of Kupffer cells having no effect on during the establishment and initial growth of tumors would suggest a modest role in tumor establishment during this early phase; the fact that the modest difference in tumor growth seen at day 16 was not evident at day 21 would suggest this is a transient effect.[10] Collectively, the data in the present studies provides a fascinating insight into how the resident macrophages of the liver can regulate tumor growth.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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