Chemokines and Cancer: Friends or Foes?

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Received date: June 08, 2020; **Accepted date:** June 22, 2020; **Published date:** June 29, 2020

Abstract

Immune cell infiltration into tumors, intratumoral cellular organization, and the cell-specific expression patterns of chemokines and *

attributed to the expression of CXCR4 on MDSCs and the upregulation of CXCL12 within the tumors [5,8]. In a mouse glioma model, the administration of anti-CXCR4 antibody decreased tumor infltration of MDSCs and in combination with anti-PD-1 antibody improved overall survival [5,9]. Building on this fnding, a still ongoing Phase II clinical trial of the CXCR4 antagonist BL-8040 in combination with the anti-PD-1 antibody pembrolizumab in the treatment of pancreatic ductal adenocarcinoma (NCT02826486) found that objective response rate, overall survival, and disease control rate were all improved in patients that received the combined drug regimen [10]. Perhaps lending insight into the mechanism of this outcome, it was noted that BL-8040 increased CD8+ efector T cell tumor infltration, decreased MDSCs, and decreased circulating regulatory T cells [10].

In the sera of colorectal cancer patients there is a noted increase in CCL15 and a striking intratumoral presence of MDSCs expressing its receptor CCR1 [5]. To explore the causative mechanism connecting these observations with tumor growth, CCL15 was genetically deleted from a human colorectal cancer cell line and implanted in an orthotopicxeno graf model. In this study it was concluded that CCL15 deletion was associated with diminished CCR1+ cell accumulation in the tumor and limited tumor growth [11]. Interestingly, analysis of 333 clinical specimens of primary colorectal cancer showed that CCL15 was expressed mainly at the invasion front, rather than the center of the tumor. T is suggests that MDSCs may form a cellular barrier of immunosuppression, preventing T cell infltration and function at the tumor boundaries. T is again calls to mind the importance of cellular organization within the tumor microenvironment.

T e CXCR1 and CXCR2 axes, including the ligands CXCL1, CXCL2, CXCL5, and CXCL8, also contribute to migration and recruitment of MDSCs [5]. In particular, CXCL8 which binds both CXCR1 and CXCR2 has been heavily implicated in malignant melanoma tumor progression [12-16]. Together this suggests that CXCR1 and CXCR2 inhibition is an attractive intervention strategy for malignant melanoma. A currently recruiting Phase I clinical trial (NCT03161431) will treat participants with melanoma for 21 days with SX-682, a CXCR1/2 inhibitor, as a monotherapy - then with pembrolizumab, an FDA approved immunotherapy for melanoma. All

Conficts of Interest

None

Acknowledgment

T is work was supported by grants from the NIH (AI25640 and CA231277) and from the Cancer Research Institute.

References

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