Analysis of the transcriptome of circulating Ly6C(hi) monocytes reveals JAM-A as a novel marker of tumor-induced monocyte reprogramming

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Background: Tumor-associated macrophages (TAMs) have been shown to promote tumor progression and resistance to anticancer therapies in a wide range of malignancies. Therefore, therapeutic approaches which prevent TAM accumulation are an emerging field of interest. TAMs primarily originate from circulating Ly6C(hi) classical monocytes which are recruited to tumors and differentiate into macrophages in response to local stimuli. In the current study, we aimed to understand how the phenotype of circulating monocytes changes in cancer and identify tumor-induced surface markers or pathways which could be targeted to prevent monocyte recruitment and subsequent TAM accumulation at the tumor site.
Methods: We performed transcriptomic analysis via RNA-sequencing in Ly6C(hi) monocytes from naive and tumor-bearing mice in 3 tumor models, including Lewis lung carcinoma, TSA breast carcinoma and MMTV-PyMT breast carcinoma. Selected genes which showed tumor-induced upregulation in all tumor models were validated using flow cytometry as well as in vitro and in vivo functional assays.
Results: We found that tumors induced extensive transcriptional changes in circulating Ly6C(hi) monocytes which showed overlap across different tumor types and resulted in the upregulation of genes primarily involved in the regulation of cell migration. Among the top tumor-induced genes, we identified F11r which encodes the membrane protein Junctional Adhesion Molecule-A (JAM-A). We observed that only a small subset of circulating Ly6C(hi) monocytes expressed JAM-A protein in the steady-state and this JAM-A+ population significantly expanded during tumor progression. This process was driven by the pro-inflammatory cytokine IL-1β. Importantly, tumor-induced upregulation of JAM-A was restricted to Ly6C(hi) and Ly6C(lo) monocytes among circulating immune cells. Deletion of JAM-A in Ly6C(hi) monocytes impaired their migration towards the chemokine CCL2, suggesting that JAM-A expression promotes the establishment of a migratory monocyte phenotype.
Conclusions: Overall, our study demonstrates that circulating Ly6C(hi) monocytes undergo extensive tumor-induced reprogramming before reaching the tumor. Our results establish JAM-A as a novel surface marker which could be used to identify and target tumor-educated monocytes in the circulation.

Keywords : JAM-A, IL-1, migration, monocyte, tumor-associated macrophage
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