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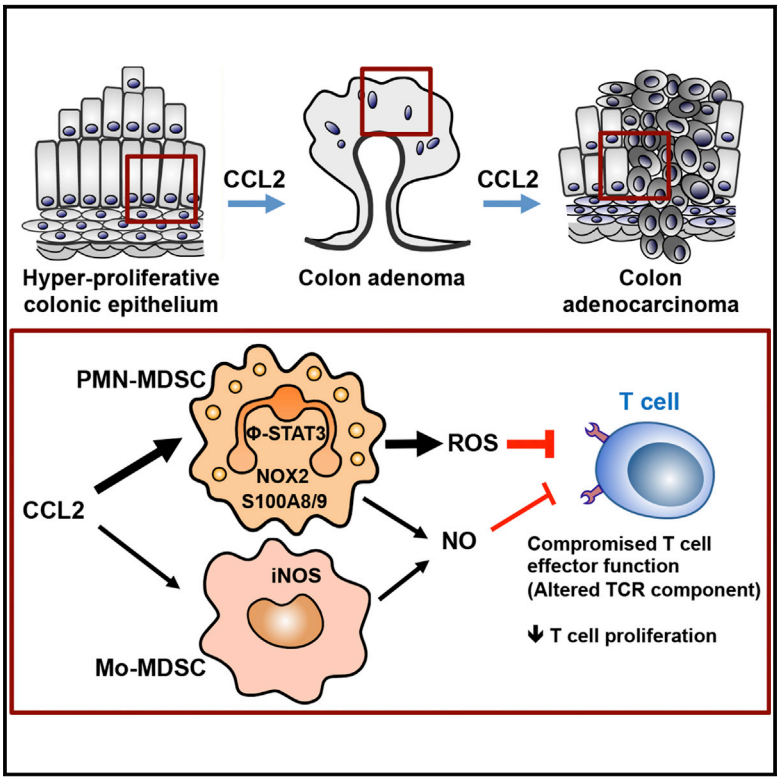
CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function

Graphical Abstract



Highlights

- CCL2 is elevated in human dysplastic colon lesions, adenoma, and adenocarcinoma
- CCL2 affects MDSC accumulation and function in colonic carcinogenesis
- CCL2 modulates T cell suppression of PMN-MDSCs in a STAT3-mediated fashion
- CCL2 neutralization re-shapes the tumor microenvironment, halting colon cancer

Authors

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In Brief

Chun et al. have found that CCL2 promotes colorectal carcinogenesis by influencing MDSC accumulation and function and shaping a tumor-permissive tissue microenvironment. This works suggests that CCL2 and MDSCs represent effective therapeutic targets for colon cancer prevention and interception.

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CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function

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SUMMARY

Our study reveals a non-canonical role for CCL2 in modulating non-macrophage, myeloid-derived suppressor cells (MDSCs) and shaping a tumor-permissive microenvironment during colon cancer development. We found that intratumoral CCL2 levels increased in patients with colitis-associated colorectal cancer (CRC), adenocarcinomas, and adenomas. Deletion of CCL2 blocked progression from dysplasia to adenocarcinoma and reduced the number of colonic MDSCs in a spontaneous mouse model of colitis-associated CRC. In a transplantable mouse model of adenocarcinoma and an *APC*-driven adenoma model, CCL2 fostered MDSC accumulation in evolving colonic tumors and enhanced polymorphonuclear (PMN)-MDSC immunosuppressive features. Mechanistically, CCL2 regulated T cell suppression of PMN-MDSCs in a STAT3-mediated manner. Furthermore, CCL2 neutralization decreased tumor numbers and MDSC accumulation and function. Collectively, our experiments support that perturbing CCL2 and targeting MDSCs may afford therapeutic opportunities for colon cancer interception and prevention.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States (Tenesa and Dunlop, 2009). CRC includes hereditary, sporadic, and colitis-associated colon cancer. Inflammatory bowel disease (IBD) is associated with an increased risk of developing IBD-associated CRC (Itzkowitz, 2003). Chronic inflammation plays a key role in tumor initiation in colitis-associated CRC. Although other types of CRC develop without any signs of macroscopic inflammation, robust infiltration of multiple immune cells is a common feature of sporadic CRC.

Immune cells play a central role in the tumor microenvironment (Hanahan and Coussens, 2012). CRC involves imbalanced Th1/Th17/Th2 responses (Galon et al., 2013), altered innate lymphoid cell activity (Pearson et al., 2012), and enhanced immunosuppressive regulatory T cells and tumor-associated macrophages (TAMs) (Kang et al., 2010). Accumulating evidence supports that myeloid-derived suppressor cells (MDSCs) contribute to cancer immune evasion by suppressing T cell anti-tumor functions and modulating innate immune responses (Gabrilovich and Nagaraj, 2009). MDSCs comprise a heterogeneous population of immature myeloid cells characterized by co-expression of CD11b and Gr-1 and lack features of mature macrophages and dendritic cells in tumor-bearing mice (Gabrilovich et al., 2012). MDSCs can be divided into two distinct sub-populations: monocytic MDSCs (Mo-MDSCs) and polymorphonuclear (PMN)-MDSCs, also known as granulocytic (G)-MDSCs (Gabrilovich et al., 2012). These two subsets differ in their gene expression profiles and immunosuppressive activities (Gabrilovich and Nagaraj, 2009). In many cancers, including CRC, blood MDSC numbers correlate with stage and metastatic burden (Diaz-Montero et al., 2009). However, factors regulating MDSC subset accumulation and MDSC's distinct contributions to CRC development remain underexplored.

Chemokines, which recruit immune cells to inflamed sites, contribute to the pathogenesis of colitis and colon cancer. CCL2, a member of the C-C chemokine family, regulates the recruitment of myeloid cells into inflamed sites and tumors. CCL2-mediated macrophage recruitment promotes tumor growth, progression, and metastasis in breast, ovarian, and prostate cancers (Fader et al., 2010; Qian et al., 2011; Zhang