Restoring inflammatory balance as a potential preventive strategy for inflammation induced cancer

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In contrast to the accepted notion that tumor-derived signals polarize macrophages toward a protumorigenic M2 phenotype during tumor progression, we recently discovered that the inflammatory microenvironment is capable of restoring inflammatory balance as a potential preventive strategy for inflammation-induced cancer. This phenomenon is achieved by promoting macrophage polarization to a tumor-suppressing phenotype through the modulation of c-Jun phosphorylation. In this study, we found that c-Jun was upregulated in inflammatory cells within the liver, implicating a role for this key transcription factor in the regulation of macrophage phenotype during tumor progression. Further analyses revealed that JNP facilitates macrophages polarization toward the protumorigenic M2-like phenotype by regulating the expression of chemokines and cytokines. These findings suggest that JNP plays a role in macrophages rather than hepatocytes during inflammation-induced HCC, an interpretation in accordance with accumulating results from clinical studies that show a strong correlation between macrophage density and poor patient prognosis.

Notably, analyzing isolated liver macrophages along the time-course of hepatitis in Mdr2−/− mice indicated that the phenotypic switch of liver macrophages was controlled by JNP prior to tumor initiation and not only along the course of tumor progression as a response to tumor-derived educating signals. Indeed, we revealed that JNP mediates Treg accumulation in the inflammatory environment, based on 2 different in vivo models of inflammation and demonstrated that JNP dictates Treg recruitment to the inflammatory microenvironment at the premalignant stage before the onset of HCC.

Currently, we do not fully understand how macrophages switch from a tumor suppressing to a tumor promoting phenotype along the course of neoplastic disease. Several transcription factors and cellular signaling pathways have been proposed to

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The inflammatory microenvironment is a key component of tumors. Among various inflammatory cell types, macrophages are prevalent in both murine and human tumors. Macrophages are remarkably plastic functionally and can alter their phenotype in response to signals originating from their microenvironment. They can be polarized toward either one of 2 extremes of a phenotypic continuum termed M1 and M2 macrophages. Whereas classically activated M1 macrophages produce Type I pro-inflammatory cytokines, participate in antigen presentation and play an antitumorigenic role, M2-polarized macrophages produce Type II cytokines, promote anti-inflammatory responses and have protumorigenic functions. More specifically, among the latter are immunosuppression, promotion of tumor angiogenesis and tissue remodeling. Multiple intermediate states along this phenotypic continuum are observed among macrophages in different states.

Recently, we studied the role of c-Jun N-terminal phosphorylation (JNP) in inflammation-associated HCC, using Mdr2 deficient mice (Mdr2−/−) – a model for inflammation-induced HCC. Surprisingly, we discovered that whereas elimination of JNP at serines 63 and 73 via germ line replacement of serines with alanines, results in a dramatic reduction of inflammation-induced HCC, deletion of c-Jun only in hepatocytes had no effect on tumor frequency and size. In accordance, we found that c-Jun was upregulated in parenchymal inflammatory cells within tumors, reinforcing the notion that JNP exerts its protumorigenic phenotype via the inflammatory microenvironment. Importantly, in human HCC, JNP was mainly detected in inflammatory cells rather than in malignant hepatocytes. In addition, genetic prevention of JNP reduced macrophage density and attenuated acquisition of the M2 phenotype. Further analyses of another inflammation model in vitro and in vivo revealed that JNP facilitates macrophages polarization toward the protumorigenic M2-like phenotype in a cell autonomous manner, without affecting M1 polarization. We also discovered that JNP proficient M2-like macrophages overexpressed the (C-C motif) chemokines CCL17 and CCL22, both of which are known as chemotactic factors for immunosuppressive regulatory T cells (Tregs), providing a possible mechanistic explanation for the protumorigenic function of the M2-like macrophages in HCC. These findings led us to
be involved in regulating recruitment and differentiation of tumor-associated macrophages (TAMs), including nuclear factor kappa B (NF-κB), signal transducer and activation of transcription 3 (STAT3), and hypoxia-inducible factor 1α (HIF1α). A recent study showed that lactic acid, a glycolytic by-product of tumor cells, can induce macrophage M2-like phenotype among TAMs by stabilizing HIF1α under normoxic conditions. Another recent study found that inhibiting colony stimulating factor 1 receptor (CSF-1R) in a glioblastoma model induced an M2 to M1 switch thereby resulting in tumor regression. Our findings add to this bulk of knowledge the identification of JNP as a key mediator of macrophage education during inflammation-induced cancer and point to recruitment of immunosuppressive Tregs as a possible effector protumorigenic mechanism (Fig. 1).

It is well accepted that the macrophage phenotypic switch from anti-to protumorigenic M2 is mediated by signals that emanate from tumor cells, hence the commonly used term “tumor educated macrophages.” Our study proposes a complementary scenario, which may be operative in chronically inflamed tissues: persistent inflammatory cues can elicit acquisition of a protumorigenic M2-like phenotype. This can create a tumor favorable environment that precludes effective early tumor elimination/surveillance at the premalignant stage. Thus we hypothesize that chronic inflammation (at least in the liver) can progress from an early anti-tumorigenic phase to a late protumorigenic phase (Fig. 1). This suggests that immune check point drugs (which work by invigorating antitumor immunity) may be an effective strategy for tumor prevention in inflammation-induced cancers, where a late protumorigenic phase is observed. Specifically, it sets the stage for testing the possibility that immune activation can prevent hepatitis-associated HCC in high-risk individuals as determined by classification of the inflammatory infiltrate in the liver.

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