Tumor progression is tightly regulated through the coordinated actions of intrinsic genetic modifications and extrinsic environmental effects.1 Cancer stem cells (CSCs) have emerged as both the cell-of-origin, often underlying tumor initiation, and as key drivers of malignant disease progression. Accumulating evidence has unveiled robust and supportive contributions of the tumor microenvironment (TME) to the survival, self-renewal and tumorigenic activities of CSCs.2 In particular, tumor-infiltrating stromal cells, such as fibroblasts and macrophages, have been shown to play critical roles in promoting the tumorigenic activities of CSCs.3,4 However, how the functional and phenotypic heterogeneity of the CSCs themselves, in turn, impacts the pathophysiological activities of tumor-infiltrating stromal cells remains largely unknown. Conversely, cellular stresses imposed by environmental insults may exert profound consequences on the functional properties of CSCs and affect the mode of interaction between tumor cells and tumor-infiltrating stromal cells. Responses to cytotoxic chemotherapies represent typical environmental stresses encountered by tumor cells and the TME, and the development of chemoresistance may alter tumorigenicity by re-wiring genetic and epigenetic pathways thereby changing the functional properties of CSCs. Moreover, the alteration of CSC functions by chemoresistant niches may translate into modification of the tumorigenic activities of tumor-associated stromal cells. Consistent with these assumptions, we recently found that resistance to cytotoxic chemotherapy renders CSCs capable of creating immunosuppressive niche environments. The CSCs arising from chemoresistant tumors (i.e., chemoresistant CSCs) have the unique ability to promote macrophage-colony stimulating factor (CSF1, or better known as M-CSF,) secretion, a cytokine that generates M2-type macrophages.5-7,13-15 Consequently, chemoresistant CSCs promote M2 macrophage differentiation through interferon-regulatory factor-5 (IRF5)- and macrophage-colony stimulating factor (M-CSF)-dependent mechanisms and produce various other cell-signaling factors that together fuel inflammation-driven carcinogenesis. These findings clarify a molecular pathway linking cancer “stemness” and pro-tumor inflammation in an immunosuppressive niche.

Keywords: cancer stem cells, chemoresistance, macrophage, inflammation-driven cancer, IRF5

Abbreviations: CSC, cancer stem cells; IRF5, interferon-regulatory factor-5; ISRE, interferon-stimulated regulatory element; M-CSF, macrophage-colony stimulating factor; TAM, tumor-associated macrophage; TME, tumor microenvironments; NF-κB, nuclear factor-kappaB

We identify novel mechanisms whereby chemoresistance enables cancer stem cells to create pro-inflammatory tumor microenvironments. Chemoresistant cancer stem cells promote M2 macrophage differentiation through interferon-regulatory factor-5 (IRF5)-and macrophage-colony stimulating factor (M-CSF)-dependent mechanisms and produce various other cell-signaling factors that together fuel inflammation-driven carcinogenesis. These findings clarify a molecular pathway linking cancer "stemness" and pro-tumor inflammation in an immunosuppressive niche.
M-CSF remain to be resolved. However, unique, genotoxic, stress-induced systems stimulated by ISRE-mediated inflammatory cascades are essential for IRF-5 activation in chemoresistant CSCs.

It is noteworthy that chemoresistant CSCs have an enhanced ability to produce multiple sets of inflammatory mediators in addition to M-CSF, including the interleukins IL-1β, IL-6 and IL-8, and the C-C-L family chemokine CCL2, etc., in an NF-κB-dependent manner. NF-κB-mediated inflammatory signals that occur in response to chronic genotoxic stimuli lead to overtly pro-inflammatory programs that have been established as critical signaling hubs linking tumor-associated inflammation with multiple carcinogetic processes. For example, CCL2 produced by chemoresistant CSCs recruits CCR2+ monocytes into tumor tissues, which serve as precursors of immunosuppressive TAMs. On the other hand, other CSC-R-derived inflammatory cytokines, such as IL-1β, IL-6, IL-8 and TNF-α, contribute to the generation of pro-inflammatory T helper type 17 (Th17) cells and tumor-associated neutrophils (TAN), immune cells that are acutely involved in inflammation-driven carcinogenesis and tumor angiogenesis. Therefore, it is likely that the pro-inflammatory profiles of CSCs may act beyond the generation of M2 macrophages responding to the IRF5-M-CSF signaling axis. Such CSC-derived signals in the tumor milieu may manifest inflammation-associated carcinogenesis by coordinately recruiting multiple sets of stromal cells into tumors, and further, may also induce protumorigenic properties in TMEs (Fig. 1). Clearly, additional studies are required to delineate a comprehensive overview of the full impact of the inflammatory properties of chemoresistant CSCs on tumor progression and prognosis.

Our findings that chemoresistant CSCs have the potential to generate inflammatory TMEs raise the possibility that resistance to anticancer modalities other than chemotherapy may modulate CSC phenotypes and intratumor stromal cell functions. Indeed, resistance to inhibitors targeting epidermal growth factor receptors (EGFR) or BRAF (V600E) are frequently correlated with proinflammatory signaling in the TMEs mediated through the IL-6/STAT3 signaling axis and transforming growth factor β (TGFβ) mediated pathways. Thus, it is critical to evaluate whether responses to therapies targeting oncogenic signatures that contribute to CSC activities and tumor-associated inflammation.

**Figure 1.** CSCs derived from chemoresistant tumors have unique abilities to manifest pro-inflammatory profiles. The constitutive activation of interferon-regulatory factor-5 (IRF-5) in chemoresistant tumors (CSC-R) upregulates macrophage-colony stimulating factor (M-CSF) in the tumor microenvironment and generates M2 macrophages, whereas the chemokine CCL2-2 produced by CSC-R is responsible for recruiting M2 macrophages into tumor tissues. CSC-R also promote the synthesis of the interleukins IL-1β and IL-6, key mediators of T helper cell type 17 (Th17) cell differentiation, as well as IL-8 and tumor necrosis factor α (TNFα), signals that facilitate neutrophil tumor infiltration promote and angiogenesis. These intratumoral immunologic re-wirings of the tumor microenvironment fostered by CSC-R further promote inflammation-driven carcinogenesis.
Further exploration of the molecular mechanisms by which resistance to anticancer drugs connects CSCs with inflammation-driven carcinogenesis should reveal new strategies to effectively target difficult to treat malignancies. It is also imperative to clarify how CSCs and their downstream factors and signals regulate specialized sets of immunological parameters and how this regulation correlates with responsiveness to particular types of anticancer modalities. Such information is necessary in order to identify ideal biomarkers to stratify patients according to their predicted responses to anticancer therapeutics.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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