Pancreatic cancer-associated stellate cells
A viable target for reducing immunosuppression in the tumor microenvironment

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Pancreatic cancer-associated stellate cells secrete soluble factors, such as interleukin-6 (IL-6), that promote the accumulation of myeloid-derived suppressor cells via a signal transducer and activator of transcription 3 (STAT3)-dependent mechanism. Targeting components of the IL-6/JAK/STAT3 signaling axis within the tumor stroma could therefore inhibit local immunosuppression and improve the efficacy of immunotherapeutic regimens against pancreatic cancer.

Pancreatic adenocarcinoma has a dismal survival rate of less than 5%, and a few effective therapies are nowadays available for advanced disease stages.[1] Thus, it is imperative to achieve a better understanding of the factors driving this deadly cancer and to identify areas for efficient therapeutic interventions. The pancreatic tumor microenvironment has attracted a great deal of attention due to its ability to foster a dense network of fibroblasts known as pancreatic stellate cells (PSCs). These cells have been shown not only to promote tumor cell survival and invasiveness but also to support the fibrotic response normally observed in pancreatic adenocarcinomas. Although the reciprocal relationship between PSCs and malignant cells has previously been appreciated, a few studies have examined if and how the pancreatic stroma influences immunosuppressive cell populations. Recently, elevated levels of myeloid-derived suppressor cells (MDSCs) have been associated with reduced overall survival among pancreatic cancer patients.[2] Therefore, it is important to understand the factors that promote the expansion and immunosuppressive functions of MDSCs, as these could be manipulated to improve the recognition (and possibly eradication) of pancreatic carcinomas by the immune system.

We have recently demonstrated that PSCs secrete an array of pro-inflammatory cytokines that are important for MDSC development, migration, and functions.[3] One of the most abundant among such pro-inflammatory cytokines is interleukin-6 (IL-6). This cytokine is known to regulate MDSC expansion and functions via a Janus kinase 2 (JAK2)- and signal transducer and activator of transcription 3 (STAT3)-dependent signaling pathway. Thus, supernatants from PSC cultures promoted the conversion of healthy donor peripheral blood mononuclear cells (PBMCs) into functional MDSCs (Fig. 1). Blocking IL-6 in the supernatants abrogated the accumulation of MDSCs, an effect that (largely downstream of IL-6) was dependent on STAT3 signaling. STAT3-conveyed signals were indeed required for the survival of PSCs and for them to produce IL-6. Recent results from Bayne et al. also indicate that pancreatic cancer cells themselves produce many different mediators that promote the expansion of MDSCs, including granulocyte macrophage colony-stimulating factor (GM-CSF).[4] GM-CSF might therefore synergize with the IL-6/STAT3-dependent feed-forward loop to promote both PSC survival and immunosuppression in the pancreatic tumor microenvironment (Fig. 1).

These data provide a strong rationale in support of therapies targeting the IL-6/JAK/STAT signaling axis not only within tumor cells, but also within stromal PSCs and immunosuppressive cells found in the pancreatic tumor microenvironment. Indeed, at least theoretically, reducing systemic and tumor-infiltrating MDSCs could be achieved by targeting resident PSCs. If validated in pancreatic cancer patients, this approach might have significant implications for the enhancement of the therapeutic efficacy of immunostimulatory agents. Recently, immunotherapeutic interventions that promote T cell-mediated antitumor immune responses, such as monoclonal antibodies targeting CTLA-4 (ipilimumab), PD-1, or PDL-1 as well as stimulators of innate immunity (e.g., Toll-like receptor agonists, heat-shock proteins, cytokines, etc.), have been associated with an impressive clinical activity in advanced cancer patients.[5,6] Indeed, the clinical benefit of immunostimulatory interventions may be limited by the elevated levels of immunosuppressive
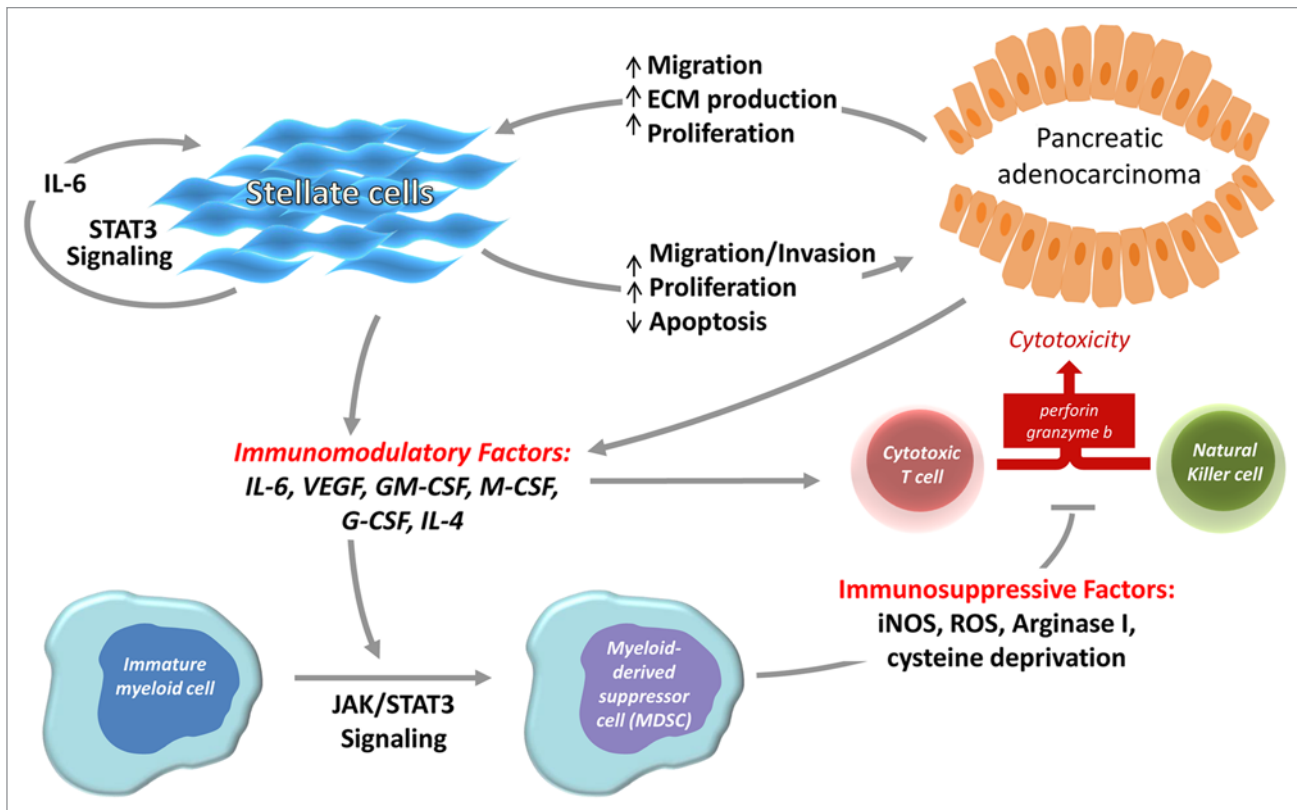
Figure 1. Pancreatic cancer-associated stellate cells promote an immunosuppressive tumor microenvironment. Pancreatic stellate cells secrete inflammatory factors and cytokines including interleukin-6 (IL-6), which not only is essential for their survival but also stimulates its own secretion in a feedforward signaling loop mediated by Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3). These inflammatory mediators also promote the expansion of myeloid-derived suppressor cells (MDSCs) in a STAT3-dependent fashion. MDSCs accumulate in the pancreatic tumor microenvironment and suppress antitumor immune responses, thus favoring tumor cell survival and disease progression.

cells and cytokines present in patients with advanced tumors. Our results point to PSCs as to an important driver of immunosuppression within the tumor microenvironment.

Further investigation is required for determining possible genetic factors that influence how stromal cells become activated and secrete the panel of inflammatory cytokines that promote immunosuppression. Others have shown that that genetic inactivation of tumor suppressor genes such as *PTEN* in stromal fibroblasts can accelerate the malignant transformation and progression of epithelial tumors due to the overexpression of a host of pro-inflammatory genes.[7] Therefore, identifying the genetic drivers of the inflammatory phenotype of PSCs could yield important clues to limit the desmoplastic reaction that is so prominent in pancreatic cancer and other malignancies.

In the normal pancreas, stellate cells typically exist in a quiescent/naïve state, containing vitamin A/lipid droplets and producing extracellular matrix (ECM) components. In contrast, during injury, inflammation or cancer, these cells become activated, a process that is accompanied by the loss of vitamin A stores. At this point, PSCs assume a myofibroblast phenotype characterized by enhanced proliferation and ECM component production, as well as by the secretion of numerous inflammatory and immunosuppressive cytokines.[3,8] This inflammatory microenvironment may be further exacerbated by a number of factors released from cells dying in response to chemotherapy or antitumor immune responses. In this context, of particular interest is the emission of damage-associated molecular patterns including high mobility group box 1 (HMGB1) and ATP.[9] Importantly, it has

been recently been shown that HMGB1 promotes an advanced glycosylation end product-specific receptor (AGER, best known as RAGE)-dependent inflammatory pathway that stimulates pancreatic tumor growth.[10] The elucidation of the role of factors such as HMGB1 and other damage-associated molecular patterns in both pathological and physiological settings will surely help our understanding of how to target the (pancreatic) tumor microenvironment.

In conclusion, our data provide further rationale for targeting specific aspects of the pancreatic cancer stroma. For instance, inhibiting inflammatory cytokines such as IL-6 could lead to the reduction of immunosuppressive cell populations and hence increase the efficacy of antitumor immunotherapeutic regimens. Targeting the stromal compartment of the pancreatic tumor microenvironment

could indeed lead to the design of efficient immunotherapeutic interventions against this deadly neoplasm.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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