

Role of Stat3 in mediating the crosstalk between tumor and immune cells

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Abstract

My lab has shown that Stat3, an oncogenic protein constitutively-activated in tumor cells, is also persistently activated in tumor stromal cells, including diverse immune subsets. We have further demonstrated that Stat3 signaling coordinates multiple levels of interactions between tumor cells and their microenvironment, affecting tumor growth, apoptosis and angiogenesis. Importantly, our recent studies revealed that oncogenesis itself coordinates cancer immune evasion/suppression: constitutively-activated Stat3 inhibits expression of certain "danger" signals necessary for immune activation, and conversely, inhibiting Stat3 in tumor cells allows activation of both innate and adaptive anti-tumor immunity. We have also shown that Stat3 activity in tumors promotes production of immune suppressive factors, including VEGF and IL-10, that activate Stat3 in various immune cells in the tumor microenvironment. Tumor-induced Stat3 activation in multiple hematopoietic cell types restrains tumor immune responses, thus defining a second level through which Stat3 signaling inhibits the generation of anti-tumor immunity. Constitutively-activated Stat3 in dendritic cells (DCs), Gr-1+CD11b+ myeloid cells, NK cells and neutrophils renders them dysfunctional and/or immune suppressive. Inhibiting Stat3 in the hematopoietic system activates a multi-component, anti-tumor response. Our on-going studies also indicate that Stat3 is constitutively activated in tumor-residing T regulatory cells. Several independent studies have now shown that Stat3 activity in T cells is critical for expression of IL-10, TGF β and Foxp3, all of which are important for generating tumor T regulatory cells. Taken together, these studies demonstrate that Stat3 signaling within the tumor is key to mediating the immune suppression in the tumor microenvironment, and that inhibiting Stat3 abrogates tumor immune suppression and activates anti-tumor mechanisms involving diverse immune cells. Supporting this notion are our recent findings that inhibiting Stat3 in immune cells markedly increases anti-tumor effects by conventional immunotherapeutic approaches, such as CpG-based therapy.

Our recent data suggest that Stat3 signaling in tumor cells allows them to co-opt immune cells, which results in cancer progression. Tumor stromal immune cells, especially myeloid cells, are major producers of growth, angiogenic and invasive factors. The concept of targeting both tumor cells and the tumor microenvironment for more effective therapy is gaining momentum. However, a molecular target to inhibit expression of the multitude of factors critical for angiogenesis/invasion in tumor stromal cells has not been defined. Our preliminary results show that constitutively-activated Stat3 in diverse tumor-associated hematopoietic/immune cells promotes expression of a large array of growth and angiogenic/invasive factors, many of which are also Stat3 activators, which, in turn, induce Stat3

activation in both tumor cells and tumor stromal cells. We have further demonstrated that Stat3 activity in tumor stromal immune cells promotes angiogenesis in a Stat3-dependent manner. Consequently, targeting Stat3 in tumor stromal immune cells affects the tumor microenvironment at multiple levels.

How can a single molecule contribute to so many different facets of oncogenesis? We postulate that this relates to links between cancer and wound healing. Wound healing is an essential physiological process that is very complex and highly coordinated. Therefore, it is logical that it is orchestrated by only one or few molecules. Cancer development and wound healing share many similarities, but a fundamental difference between the two is that wound healing is self-limiting whereas cancer is not. Recent studies demonstrated that Stat3 regulates numerous genes common to both wound healing and oncogenesis, and that a lack of Stat3 alleles prevents tumor development in both *Drosophila* and mice and impairs wound healing. This essential role of Stat3 in wound healing raises a critical question for cancer therapy: would systemic Stat3 inhibition cause severe side effects? In addition to numerous independent *in vitro* studies showing that a tumor cell's dependence on Stat3 for survival is much greater than that of normal cells, we and others have shown that induced Stat3 gene ablation in the entire hematopoietic system in adult mice has no detectable consequences on survival and function of these cells. On the contrary, Stat3^{-/-} bone marrow cells can reconstitute irradiated syngeneic recipients, and inhibit tumor growth. Nevertheless, prolonged Stat3 ablation in the hematopoietic system can cause autoimmune disease. To avoid autoimmune disease and other potential side effects that might be associated with long-term systemic Stat3 inhibition, it is highly desirable to direct Stat3 antagonists to tumor and tumor-draining lymph nodes. In addition, oncogenic potential and constitutive Stat3 activation are restricted to normal cells within the tumor microenvironment. For example, tumor T regulatory cells, but not splenic T regulatory cells, suppress anti-tumor immunity and display constitutively-activated Stat3. Therefore, the anti-tumor effects of inhibiting Stat3 will benefit most from targeting Stat3 in the tumor. How can we facilitate the delivery of Stat3 antagonists to tumor cells and tumor stromal cells, while simultaneously avoiding their inhibiting cells in normal organs? We propose a nanoparticle delivery can solve this problem. Because Stat3 is constitutively activated in tumor-associated hematopoietic cells, but not in their normal splenic counterparts, we predict that it is feasible to identify biomarkers unique to tumor-associated normal cells, thereby allowing targeting of multiple types of tumor stromal cells as well as tumor cells using the same nanoparticle(s).