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The potential for targeting the STAT3 pathway as a novel therapy for melanoma

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Melanoma is the most deadly form of skin cancer, and the worldwide incidence of this malignancy is rising faster than that of any other cancer. Few effective therapies are available for patients with advanced disease, although a number of recent advances provide some hope for an improvement in clinical outcomes. In particular, small-molecule inhibitors of mutated *BRAF* have produced dramatic clinical responses in the approximately 50% of melanoma patients who harbor this mutation in their tumor. Unfortunately, the remaining patients who do not have this mutation receive no benefit from this class of drugs. Most patients receiving these agents eventually recur and succumb to disease within the course of only a few months [1]. Overcoming *BRAF* inhibitor resistance is, therefore, a very active area of research. In this regard, several ongoing human clinical trials seek to combat *BRAF* inhibitor resistance by combining these agents with small molecules targeting MEK, PI3K and other relevant signal transduction pathways.

Melanoma is also traditionally thought of as a tumor that is highly responsive to immune-based therapies. Although the precise mechanisms of action remain unknown, immunotherapy with recombinant cytokines (IFN- γ and IL-2) or checkpoint blockade in T lymphocytes with antibodies targeting CTLA4 or PD1–PDL1 interactions can elicit durable, complete responses in some patients [2]. These data suggest that a potentially beneficial approach to therapy for melanoma would be to identify agents or drug-gable pathways that might act directly upon the malignant cells and upon the immune system in patients. Indeed, dysregulated immune function in patients with melanoma and other malignancies is becoming recognized as a therapeutic target and a hallmark of cancer in general.

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One target of particular interest for melanoma is the STAT3 protein. STAT3 is a transcription factor that is frequently phosphorylated on tyrosine 705 at basal levels in melanoma cells, and can be activated in response to a variety of extracellular ligands [3]. There are multiple redundant mechanisms leading to STAT3 phosphorylation, dimerization and translocation to the nucleus to drive oncogenic gene expression patterns in melanoma cells. These include extrinsic growth factors and cytokines (IL-6 and VEGF) or intrinsic changes, such as mutation of oncogenic pathways (e.g., *Src*) that reside upstream of STAT3. In melanoma cells, STAT3 has been shown to be required for survival and is thought to represent a key player in promoting metastasis, angiogenesis, immune evasion and a cancer-initiating cell phenotype [3–5]. Importantly, although deletion of the *STAT3* gene in mice is found to be embryonic lethal, conditional knockout mice lacking STAT3 in individual tissues are viable. It is thought that, although required during embryogenesis, STAT3 is largely dispensable in normal, fully differentiated somatic cells [6,7]. In addition, STAT3 is a critical factor that regulates the differentiation and function of immunosuppressive cell subsets present in patients with advanced cancer, including myeloid-derived suppressor cells or regulatory T cells [8]. Together these data suggest that STAT3 represents an important therapeutic target in melanoma, owing to its dual effects on both malignant cell growth and host immune function.

Although robust programs of drug development have been successful for targeting Jak2, development of clinically useful small molecules that inhibit STAT3 has been quite limited. This is due to a variety of factors, including the hydrophobic nature of the SH2 domain of STAT3, as well as issues with the suitability of the scaffolds used for inhibitors and limited pharmacokinetic properties [9]. Adding further to the complexity of this target is the fact that there is a high degree of homology between oncogenic STAT3 and other STAT proteins. This increases the potential for off-target effects.

To date, a number of strategies for inhibition of the STAT3 pathway have been evaluated for melanoma in the preclinical setting. Some approaches have focused on inhibiting upstream kinases, such as Jak2, while others have focused on targeting the STAT3 protein directly using siRNA, shRNA vectors, small molecules, platinum-based compounds or peptide aptamers [8,10]. Finally, other studies have discovered that the STAT3 signal transduction pathway is an important target of various natural products and pharmaceutical drugs intended to target other key oncogenic pathways or processes (i.e., sunitinib) [11]. Although a comprehensive description of each of these approaches is beyond the scope of this editorial, two common themes emerge. First, regardless of the approach used, targeting STAT3 leads to consistent and reproducible growth inhibitory and/or proapoptotic effects on malignant cells. Second, inhibition of STAT3 appears to be an effective means for augmenting immune-mediated tumor recognition. This transcription factor plays an important role in regulating the cytokine-mediated differentiation of myeloid-derived suppressor cells, limiting dendritic cell maturation, and promoting M2 macrophage differentiation and regulatory T-cell expansion. Several eloquent studies in preclinical melanoma models have demonstrated that inhibition of STAT3 can augment the response to anti-tumor cytokines such as IFN- γ [12], enhance the response to innate immune stimuli, such as CpG oligodeoxynucleotide [13], or augment the functional ability of adoptively transferred CD8⁺ T lymphocytes to elicit anti-tumor activity *in vivo* [14]. In agreement with these findings, studies by our group and others have shown that specifically targeted small-molecule inhibitors of STAT3 do not adversely affect the responsiveness of immune cells to clinically relevant cytokines, such as IL-12, IFN- γ , IL-2 or IFN- α [12,15,16]. Together, these data suggest that STAT3 inhibition represents an approach that may be useful in reversing immune suppression associated with melanoma and potentially in enhancing immune-based therapy against this disease.

Of particular relevance to clinical therapy of melanoma are recent data demonstrating that STAT3-targeted therapies are effective in cells that have acquired resistance to the BRAF inhibitor vemurafenib. In one recent study, Liu *et al.* demonstrated that FGF2 secretion from melanoma cells, keratinocytes or other cells in the tumor microenvironment can lead to upregulated STAT3–PAX3 signaling and vemurafenib resistance in melanoma cells. Treatment with a STAT3 inhibitor or silencing *STAT3* via siRNA was effective at inhibiting growth in both vemurafenib-sensitive or vemurafenib-resistant melanoma cells [17]. Adding further support to STAT3 as a rational target in melanoma to compliment BRAF-targeted therapy is a recent report showing that STAT3 is a central regulator of *BRAFV600E*-mediated *Mcl-1* transcription, and melanoma cell survival [18]. Finally, a third study nicely demonstrated that the EGFR–SFK–STAT3 signaling pathway was upregulated in cells with acquired resistance to vemurafenib [19]. Single-agent inhibition of Jak2 is also emerging as a therapeutic strategy, and may have a role as an indirect means of targeting the STAT3 pathway. This approach has been well tolerated in clinical trials of hematologic malignancy, polycythemia vera, rheumatoid arthritis and myelofibrosis, and is in early phase clinical trials for patients with solid tumors [20]. Therefore, it may be feasible to evaluate the effect of Jak2 inhibitor combinations in preclinical studies and rapidly generate data in support of clinical trials with these agents. Together, these data suggest that parallel inhibition of MAPK and Jak2–STAT3 signaling pathways deserves investigation to maximize direct inhibitory effects upon melanoma cells.

Despite these intriguing preliminary data, it is also important to emphasize that pursuit of parallel pathway inhibition in the clinic needs to be supported by adequate preclinical research, as well as robust correlative laboratory studies within subsequent human clinical trials. Indeed, the molecular profile of melanoma is highly heterogeneous, and it will be important to ensure genetic signatures predicting response and/or resistance to these pathway-targeted therapies are taken into consideration. Equally important will be a thorough evaluation of how these inhibitors alter immune cell phenotype and function, and to delineate how these agents will interact with other pathway inhibitors or how they will act in patients that have been heavily pretreated.

Overall, it is a very critical time in melanoma research, where many initial advances in treatment have provided a firm foundation for improvement. We are now faced with the challenges of overcoming resistance to targeted agents, and determining the best ways to employ immunotherapy for this disease. It is possible that developing effective strategies to target STAT3 will aid in our progress to overcome both of these challenges.

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