Exploring the Role of Signal Transducer and Activator of Transcription Protein-3 in Melanoma

STATs have been implicated in the genesis and progression of various cancers. The latest research explores the role of STAT3 in melanoma.

STAT proteins or Signal transducer and activator of transcription proteins, regulate key cellular functions including survival, proliferation, and differentiation. First identified in the early 1990’s, a total of seven of these cytoplasmic transcription factors have been recognized: STAT1, STAT2, STAT3, STAT4, STAT5a, and STAT5b. Due to their crucial role in cell proliferation and differentiation, STATs have been investigated for possible rules in oncogenesis and/or tumor proliferation. Both STAT3 and STAT5 have been shown to contribute to malignant cellular transformation through dysregulation of signaling pathways. STAT1, STAT3, and STAT5 have been shown to be activated by certain oncogenes and to subsequently induce malignant transformation.

STAT3 has been implicated in immune suppression by inhibiting immunostimulatory molecules and promoting expression of immunosuppressive factors. Research specific to melanoma suggests a role for STAT3 in the disease process, and researchers suggest the protein could be an important marker of malignant transformation and may possibly become a therapeutic target.

STAT3 and Cancer

Ample evidence indicts STAT3 in tumor transformation and progression. Among recent findings is new evidence implicating STAT3 in tumor growth in glioblastoma multiforme. From a human GBM cell line, Dasgupta et al developed clones expressing a dominant negative mutant STAT3 (DN-STAT3). The tumor-generating potentials of these clones and of parental and control cells were examined in immune-compromised mice. Tumors derived from the DN-STAT3 line failed to grow beyond 2mm of thickness, whereas unmodified tumor cells grew steadily.

STAT3 is now associated with myeloid cell-dependent tumor angiogenesis, due to recent evidence confirming the activity of STAT3 in mouse models of tumorgenesis.

STAT3 and Melanoma

A study published last summer supported a role for STAT3 expression in melanoma that is progressing. Researchers analyzed expression of phosphorylated STAT1 (pSTAT1) and phosphorylated STAT3 (pSTAT3) in various biopsy samples from compound nevi, dysplastic nevi, congenital nevi, primary melanoma, and sentinel lymph node metastasis. Normal melanocytes and benign nevi expressed little pSTAT1 or pSTAT3, however six of 14 biopsies from primary cutaneous melanoma and 16 of 26 biopsies from patients with melanoma metastatic to the lymph nodes showed activated pSTAT3. In contrast, just six of 23 samples from metastatic melanoma patients showed activated pSTAT1.

In a larger study, researchers recently investigated the actions of STAT3 and STAT1 in atypical nevi by analyzing pSTAT1 or pSTAT3 signaling in biopsy samples from 168 atypical nevi from 42 patients. The patients were receiving either high- or low-dose IFNalpha (HDI and LDI). The authors explain that pSTAT1 and pSTAT3, “oppose one another in biological function,” therefore they used double-immunohistochemistry for the sample analyses. As the degree of atypia of nevi increased, so did the percentage of pSTAT3-positive melanocytes.

HDI and LDI both influenced the expression of STAT1 as well as STAT3. In the junctional component of nevomelanocytic lesions, interferon downregulated the percentage of STAT3-positive melanocytes while upregulating the percentage of STAT1-positive melanocytes. Therapy augmented the pSTAT1/pSTAT3 ratio. Given these findings, the team believes pSTAT3 is a potential biomarker of melanocytic transformation and progression.

A subsequent publication reported a significantly higher mean percentage of peripheral blood mononuclear cells expressing pSTAT3 in patients with melanoma brain metastasis compared to healthy controls. Their findings confirmed the anti-STAT3 action of a novel agent WP1066, suggesting that the agent’s T-cell activation effects are secondary to inhibition of regulatory T-cells.

Finally, researchers have presented additional evidence for their early findings that STAT3 could play a role...
Signal Transduction and STATs

Benekli, et al describe the action of STATs in signal transduction:

The interaction of a cytokine with its ligand-binding receptor alpha subunit is the first step in the formation of a signaling–competent receptor complex. This process involves the oligomerization of the ligand-bound subunit with either another subunit or a separate, signal-transducing beta subunit. This oligomerization initiates the process of signal transduction by activation of the receptor-associated Janus family tyrosine kinases (JAKs) through cross-phosphorylation. Immediate targets of the activated JAKs are the cytoplasmic portions of the receptors and receptor-associated proteins. The tyrosine phosphorylated sites become docking elements for Src homology 2 (SH2)- and phosphotyrosyl-binding domain–containing proteins present in the membrane or the cytoplasmic compartment. Prominent among these are the STATs. Receptor-recruited STATs are phosphorylated on a single tyrosine residue in the carboxy terminal portion. The modified STATs are released from the cytoplasmic region of the receptor subunits to form homodimers or heterodimers through reciprocal interaction between the phosphotyrosine of one STAT and the SH2 domain of another. Following dimerization, STATs rapidly translocate to the nucleus and interact with specific regulatory elements to induce target gene transcription.


Another Marker of Interest: Estrogen

Just last month, researchers reported evidence that supports the use of estrogen receptors as a prognostic indicator in melanoma. The prospective study involved 14 patients—six men with cutaneous melanoma and one with a melanocytic nevus along with six women with cutaneous melanoma and one with a melanocytic nevus. Researchers used quantitative reverse transcriptase–polymerase chain reaction and immunohistochemical analysis ER and ERβ messenger RNA (mRNA) and ERβ protein expression in lesions and in surrounding skin. While all lesions expressed detectable levels of ER and ERβ mRNA as well as ERβ protein, levels of all markers were lower in thicker, more invasive tumors (stratified by Breslow thickness). Potentially, levels of protein expression could be used to predict risk of invasion or metastasis of lesions.


in promoting oncostatin M (OSM) resistance in stage III melanoma. Specimens from stage III melanoma refractory to common therapies revealed that 18 percent of cell lines exhibited a phosphorylation defect of STAT3.

STATus Update

The accumulated evidence reveals a role for STAT3 in various malignancies. Recent data suggests that, in particular, STAT3 plays a role in malignant transformation in melanoma. Chemohistological detection of elevated expression of pSTAT3 in atypical nevi may indicate a progression toward malignancy and could indicate a high level of risk. Further research will be able to confirm the value of pSTAT3 as a risk marker for melanoma and may support wide application of pSTAT3 screening in the near future.

The possibility that STAT3 contributes to therapeutic non-response suggests that the protein may also become a therapeutic target, though such application may come farther in the future.

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