

STAT3: A multifaceted oncogene

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Signal transducers and activators of transcription (STAT) proteins are a family of transcription factors first characterized for their role in cytokine signaling. These versatile proteins contain a site for specific tyrosine phosphorylation, a modification that results in a conformational rearrangement and dimerization through phosphotyrosine-SH2 domain interactions (1). Once activated in this manner, phosphorylated STAT protein dimers accumulate in the cell nucleus, bound to enhancer elements of target genes. STAT proteins were first characterized as intermediaries in IFN signaling, a growth inhibitory cytokine pathway involved in antiviral and innate immune responses. However, as additional members of this protein family were discovered, they caught the eyes of cancer biologists as potential mediators of growth control and possibly oncogenic events. In particular, it became recognized that STAT3 and, to a lesser extent, STAT5 were stimulated by classic growth-promoting signals, such as activated growth factor receptors. Even more compelling were the seminal observations that STAT3 was a substrate for the catalytic activity of the tyrosine kinase oncoprotein v-Src (2) and that phosphorylated STAT3 accumulated in many human cancers, leading to the hypothesis that activated STAT3 is an oncogene (3). A considerable amount of experimental and clinical observations have now confirmed such a role for STAT3, and a remarkable degree of diversity has been uncovered for the molecular mechanisms at the basis of STAT3 action. Much early work has focused on direct growth-control and cell survival targets for STAT3. Recently, STAT3 has also been implicated in some noncanonical mechanisms of tumor progression that apparently do not rely on tyrosine phosphorylation or binding of homodimers to DNA (4), possibly involving pathways in malignant cells not directly regulating gene expression. However, an increasing number of findings suggest that activated STAT3 also contributes to abrogated immunity, leading to enhanced tumor cell growth. In a recent issue of PNAS, Kasprzycka *et al.* (5) united these two concepts by providing evidence that activated STAT3 in a tumor cell contributes to both cell survival and impaired immune

surveillance by conferring properties of a T lymphocyte regulatory phenotype on a T cell lymphoma.

Stat3 and Immune Suppression

Inhibition of autoreactive T cells is an essential element of a well orchestrated immune system, and many mechanisms are devoted to the important process of maintaining tolerance. One such mechanism that operates in the periphery involves so-called T regulatory (Treg) cells that express high surface levels of CD25, a component of the IL-2 receptor, and either arise in the thymus during development or are induced in the periphery after contact with antigen (6). In addition to expression of the cell surface markers CD4 and CD25, Tregs are identified by expressing the transcription factor FoxP3 and by secreting inhibitory cytokines, such as IL-10 and TGF- β .

Tumor cells with activated STAT3 secrete immunosuppressive factors.

Kasprzycka *et al.* (5) have studied the mechanisms underlying the malignancy of anaplastic T cell lymphomas, a human tumor that is often associated with aberrant expression of an oncogenic fusion protein termed NPM-ALK. This oncoprotein is derived from a chromosomal translocation that fuses the regulatory and dimerization motifs of the nucleophosmin gene to the catalytic activity of the receptor tyrosine kinase, ALK. A consistent substrate recognized for activated ALK in this tumor is STAT3 and the importance of phosphorylated STAT3 for tumor progression has become well appreciated (7). Indeed, as has been implicated for a variety of human tumors, activated STAT3 appears to contribute to both the growth and survival of ALK⁺ lymphomas (8, 9). Now, Kasprzycka *et al.* present evidence that activated STAT3 also confers a Treg phenotype to these tumor cells, potentially contributing to their ability to evade the host's immune response.

Kasprzycka *et al.* (5) show that ALK⁺ tumor cell lines secrete the inhibitory cytokines IL-10 and TGF- β , express CD25 and FoxP3, and condition their growth medium to be immunosuppressive, capable of blocking the proliferation of normal T cells. Many of these features were found to depend on STAT3, because depletion of STAT3 levels through siRNA knockdown impaired cytokine expression and immunosuppressive potency. Moreover, secreted IL-10 appeared to contribute directly to tumor cell survival, because antibody-mediated neutralization of the cytokine or siRNA knockdown of its expression induced a significant, although somewhat modest, increased rate of apoptosis. Activated STAT3 may directly contribute to IL-10 expression, because it was found bound to an enhancer element in the IL-10 promoter. The activated ALK oncoprotein contributed to all these phenotypes, because a pharmacological inhibitor of its catalytic activity or siRNA-mediated knockdown of its expression blocked IL-10, TGF- β , and FoxP3 expression. These results provide additional mechanistic insight into how activated tyrosine kinases and STAT3 can contribute to carcinogenesis, in both a cell-autonomous and an immunomodulatory manner, and add to the growing realization that STAT3 is an attractive target for cancer therapy (7, 10).

Non-Tumor Cell Autonomous STAT3?

This work by Kasprzycka *et al.* (5) also raises a number of interesting issues. There is a growing body of evidence that impaired immune surveillance plays an important role in tumor progression (11) and that immunosuppressive cytokines secreted by tumor cells may contribute to this impairment. In fact, a number of recent studies have shown that tumor cells with activated STAT3 secrete immunosuppressive factors, such as IL-10, whereas inhibition of STAT3 leads to secretion of proinflammatory cytokines. Moreover, immunosuppression induced by tumor

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cell-secreted factors may be at least partially mediated by activation of STAT3 in cells of the innate immune system, leading to inhibition of dendritic cell maturation and T cell activation (12). Therefore, immunosuppression may be a general property of many types of tumor cells, not just T lymphomas, raising questions concerning the significance of the Treg-like phenotype of ALK⁺ lymphomas. It is also difficult to parse the importance of the apparent prosurvival activity of IL-10 on these tumor cells for the overall progression of the disease. The increase in apo-

ptosis observed when IL-10 signaling was blocked was quite modest, although it has been shown in other systems that abrogation of NPM-ALK activity or STAT3 function leads to near complete tumor regression due to massive apoptosis (8, 9, 13, 14). Moreover, the present results examined only a limited set of established tumor cell lines. Because STAT3 is a fairly promiscuous substrate for activated tyrosine kinases, if STAT3 phosphorylation confers a Treg phenotype, many T cell lymphomas might be expected to display this property. It will be critical to

evaluate the generality of this STAT3-dependent regulatory circuit in additional NPM-ALK⁺ tumor lines and in primary biopsies. Nonetheless, despite these areas for future research, this study strongly reinforces the notion that STAT3 is an attractive target for tumor therapy, both within the tumor itself as well as within infiltrating hematopoietic cells in the tumor environment. These results also raise the interesting question of a possible normal role for STAT3 in Tregs and other immunosuppressive cells of the immune system.

1. Levy, D. E. & Darnell, J. E., Jr. (2002) *Nat. Rev. Mol. Cell Biol.* **3**, 651–662.
2. Yu, C.-L., Meyer, D. J., Campbell, G. S., Larner, A. C., Carter-Su, C., Schwartz, J. & Jove, R. (1995) *Science* **269**, 81–83.
3. Bromberg, J. F., Wrzeszczynska, M. H., Devgan, G., Zhao, Y., Pestell, R. G., Albanese, C. & Darnell, J. E., Jr. (1999) *Cell* **98**, 295–303.
4. Yang, J., Chatterjee-Kishore, M., Staugaitis, S. M., Nguyen, H., Schlessinger, K., Levy, D. E. & Stark, G. R. (2005) *Cancer Res.* **65**, 939–947.
5. Kasprzycka, M., Marzec, M., Liu, X., Zhang, Q. & Wasik, M. A. (2006) *Proc. Natl. Acad. Sci. USA* **103**, 9964–9969.
6. O'Garra, A. & Vieira, P. (2004) *Nat. Med.* **10**, 801–805.
7. Inghirami, G., Chiarle, R., Simmons, W. J., Piva, R., Schlessinger, K. & Levy, D. E. (2005) *Cell Cycle* **4**, 1131–1133.
8. Zamo, A., Chiarle, R., Piva, R., Howes, J., Fan, Y., Chilosi, M., Levy, D. E. & Inghirami, G. (2002) *Oncogene* **21**, 1038–1047.
9. Chiarle, R., Simmons, W. J., Cai, H., Dhall, G., Zamo, A., Raz, R., Karras, J. G., Levy, D. E. & Inghirami, G. (2005) *Nat. Med.* **11**, 623–629.
10. Buettner, R., Mora, L. B. & Jove, R. (2002) *Clin. Cancer Res.* **8**, 945–954.
11. Dunn, G. P., Old, L. J. & Schreiber, R. D. (2004) *Immunity* **21**, 137–148.
12. Gamero, A. M., Young, H. A. & Wiltout, R. H. (2004) *Cancer Cell* **5**, 111–112.
13. Amin, H. M., McDonnell, T. J., Ma, Y., Lin, Q., Fujio, Y., Kunisada, K., Leventaki, V., Das, P., Rassidakis, G. Z., Cutler, C., *et al.* (2004) *Oncogene* **23**, 5426–5434.
14. Wan, W., Albom, M. S., Lu, L., Quail, M. R., Becknell, N. C., Weinberg, L. R., Reddy, D. R., Holskin, B. P., Angeles, T. S., Underiner, T. L., *et al.* (2006) *Blood* **107**, 1617–1623.