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Targeting STATs for cancer therapy

"Undruggable" no more

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We are in the midst of an exciting transition in the treatment of cancers, from the empirically developed non-specifically cytotoxic drugs to the era of rationally-derived molecularly targeted therapies. Over the past 15 years, our understanding of the mutations that drive cancer pathogenesis has grown enormously, which has rapidly led to the development of drugs to target the associated gene products. Almost all of this focus has been on kinases, largely tyrosine kinases that are activated by translocations, point mutations, insertions and deletions. Although this approach will continue to bear fruit for some time, there is increasing evidence that the returns will be diminishing. First, dominant activating mutations in kinases are less frequent then initially expected particularly in common human cancers, and thus the number of patient whose tumors have suitable targets may be limited. The second cause for concern is the rapid development of resistance that often occurs, arising either from mutations in the target kinase or activation of a parallel pathway. Thus, the desire to target a common convergence point of multiple pathways that directly contributes to the oncogenic phenotype is highly desirable. This goal has led to consideration of transcription factors as therapeutic targets.

So-called oncogenic transcription factors are not themselves mutated in cancer, but mediate the effects of a diverse array of activated kinases in regulating the genes that control proliferation, survival, invasion and spread that underlie malignancy. Reflecting their role in the physiological control of these processes, STAT family members, particularly STAT3 and STAT5, were found to be activated inappropriately in a wide range of human cancers. Inhibition of these proteins in cancer models shows significant therapeutic benefit; by contrast, loss of function in normal cells is well tolerated, likely due to redundancies in physiological signal transduction. Thus, STATs appear to be targets with the potential for a high therapeutic index. However, while great progress has been made in developing inhibitors to a range of kinases, the ability to target transcription factors has lagged far behind. In fact, for a variety of reasons transcription factors in general, and STATs in particular, were termed "undruggable." Kinases have well-defined pockets into which ATP binds, and into which a small organic molecule can be designed to fit. By contrast, transcription factors interact with other proteins and with DNA through interfaces with large surface area, suggesting that it would be extremely difficult to design a molecule with drug-like properties that could inhibit their function.

As increasing numbers of experimental studies provide ever-stronger support for targeting oncogenic transcription factors like STATs, novel approaches for inhibiting these proteins have emerged. In this issue of *JAK-STAT*, four papers present a range of creative and complementary strategies to targeting STATs, particularly STAT3. Although STATs lack conventional enzyme activity, they do contain clearly defined domains necessary for their function. One such motif is the SH2 domain, which allows tyrosine phosphorylated STATs to form transcriptionally active dimers. McMurray et al. discuss the efforts from their lab and others to design small molecules to specifically block this interaction.[1] The fact that the phosphopeptide sequence from STAT3 can bind to this region provides a starting point in designing such inhibitors. Clever synthetic chemistry strategies can then be used to generate phosphopeptide mimetics with therapeutic activity.

As a basic understanding of the nature of STAT transcriptional regulation emerged, it became clear that STATs not only function as dimers, but they can form tetramers as well, through an N-terminal domain. This may allow STATs to bind tandem sites with lower intrinsic affinity, permit non-tyrosine phosphorylated STATs to have transcriptional activity, and provide STATs with a more nuanced regulation of gene expression based on the magnitude of the stimulus and other biological parameters. Using a lipopeptide strategy, Timofeeva and Tarasova describe the development of N-terminal domain inhibitors that hold great therapeutic promise.[2]

The paper by Sen and Grandis highlights several novel aspects of targeting STATs.[3] First, the term "undruggable" refers to the difficulty of developing small organic molecules. These authors point out that macromolecules, particularly nucleic acids, hold great promise as therapeutic agents, with a considerable track record of safety in humans. Further, they note that another domain of STATs, the DNA binding domain, is an appealing target. Decoy oligonucleotides can allow activated STATs to be diverted from their genomic targets, and block STAT-dependent gene expression. Furthermore, to their enormous credit, the

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Grandis team truly achieved clinical translation of their strategy. They conducted a phase 0 clinical trial using decoy oligonucleotides in patients with squamous cell carcinoma of the head and neck, and demonstrated evidence of inhibition of STAT3 target genes in the tumor. This is a landmark study, and definitively refutes the notion that transcription factors cannot be targeted therapeutically.

Finally, the manuscript by Walker and Frank takes a different tack to identifying STAT inhibitors.[4] Rather than using target-based design strategies, these authors discuss the development of cell-based transcription-dependent systems that can be used to screen chemical libraries for STAT modulators. Active molecules arising from these screens may be targeting STATs directly, or may be affecting critical cellular regulators of the STAT pathway. Hits from these screens can thus provide insight into the cellular signaling network, and may reveal critical targets that might otherwise be unappreciated. This group has used this strategy to identify a small molecule inhibitor of STAT3 transcriptional activity that is now in a clinical trial in patients with chronic lymphocytic leukemia (CLL).

Of course, this is not the end of the development of STAT inhibitors for the therapy of cancer and other diseases, but rather just the beginning. Many key biological questions remain such as, what is the role of non-transcriptional functions of STATs particularly in the mitochondria or cytoskeleton, what is the relation between inhibition of STATs and activation of other pathways, and why does inhibition of STAT tyrosine phosphorylation correlate with some therapeutic responses but not others? There are also important unanswered therapeutic questions such as whether the combination of STAT inhibitors that work through different mechanisms may synergize when combined, or what are optimal therapeutic combinations of STAT inhibitors with other therapeutic modalities? Given that STAT inhibitors have now been brought to the clinic, it is likely that interest in the topics reviewed in these articles will only increase from basic, translational, and clinical investigators. In any case, with regard to targeting STATs therapeutically, it seems safe to retire the word "undruggable."

About Dr David A. Frank

Dr Frank received a BS in biology from MIT, and then received an MD and PhD in pharmacology from Yale. Dr Frank was an intern, resident and chief resident in internal medicine at Yale-New Haven Hospital, and was a fellow in medical oncology at the Dana-Farber Cancer Institute. After postdoctoral laboratory training in intracellular signal transduction at Harvard Medical School, he joined the faculty at Dana-Farber where he practices oncology and conducts laboratory research focused on understanding the role of transcriptional networks in cancer pathogenesis and developing targeted molecular therapies for patients with cancer.

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