Commentary

A sensible approach to targeting STAT3-mediated transcription

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Many cancers overexpress oncogenic proteins that drive robust tumorigenic signaling cascades which can be amenable to therapeutic targeting. However, inhibition of these proteins has been met with limited success to date, at least in part, due to the numerous feedback mechanisms driven by activation of alternative signaling pathways. To avoid the toxicities of targeting multiple receptors and oncogenic proteins, drug development focused on transcription factors is attractive. Transcription factors such as NF-κB, beta catenin and signal transducers and activators of transcription (STATs) are activated in the cytoplasm by numerous upstream signaling nodes before shuttling to the nucleus to drive transcription of mitogenic and antiapoptotic genes. Their ability to convey signaling from multiple oncogenic drivers and mediate gene expression makes them very promising therapeutic targets. An article published in November 2015 by Hong et al. in the journal Science Translational Medicine demonstrated that targeting the STAT family member STAT3 using an antisense oligonucleotide (ASO) AZD9150 resulted in potent and specific inhibition of STAT3 expression and suppression of lymphoma and lung cancer growth in preclinical models (1).

Hong et al. observed that AZD9150 efficiently depleted STAT3 mRNA levels and abrogated the growth of lymphoma and NSCLC xenograft tumors in vivo when which have both tumor-intrinsic and extrinsic effects.

The STAT3 pathway can be targeted by inhibiting upstream JAK kinases (e.g., AZD1480), STAT3 dimerization (e.g., Stattic) (5) or STAT3-mediated DNA binding (STA-21, STAT3 Decoy) (6,7). However, JAK inhibitors have resulted in anemia and thrombocytopenia in clinical trials and JAK-independent mechanisms of STAT3 activation in cancer have been reported (8). Stattic has displayed promising potential in different cancer models but has also been shown to promote increased redox reactions that can trigger off-target effects (9). To specifically target STAT3, Hong et al. investigated the inhibition of STAT3 mRNA expression and transcriptional output using ASO technology. The authors modified their STAT3 ASO with constrained ethyl residues (cET) on either side of an 8–10 base phosphorothioate-modified deoxynucleotide, which improved stability and efficacy of targeting STAT3 mRNA both in vitro and in vivo. This was a critical finding since a major limitation of prior ASOs has been their poor cellular uptake. Importantly, the authors’ cET modification to the STAT3 ASO permitted lipid-independent uptake into cell lines in vitro. Additionally, the modified STAT3 ASO did not inhibit STAT1 or STAT5 underscoring the specificity of the ASO. This is a key finding since another group of STAT3 inhibitors, the STAT3 decoy oligonucleotides, have been shown to inhibit both STAT3 and STAT1 (10,11). STAT1 plays an important role in negatively regulating cell growth (12,13); therefore, cross-inhibition of STAT1 by STAT3 decoys may diminish the antitumor effects of STAT3 blockade. However, STAT3 decoys with specificity to STAT3 alone are currently being developed (14).

Hong et al. observed that AZD9150 efficiently depleted STAT3 mRNA levels and abrogated the growth of lymphoma and NSCLC xenograft tumors in vivo when
used as a single agent. Notably, STAT3 activation has been shown to be induced by inhibitors of receptor tyrosine kinases or MEK in various oncogene-addicted solid tumor models (15-17). In one such study, RNAi-mediated inhibition of the STAT3 was sufficient to overcome erlotinib resistance (15). Furthermore, clinical testing of gefitinib and erlotinib in lung cancer demonstrated complete responses in patients with low STAT3 levels (RNA-seq) and increased recurrences in patients with high STAT3. Therefore, while AZD9150 may be potent against lymphomas as a monotherapy, combination of AZD9150 with other oncogenic targeting agents may be a promising therapeutic approach against solid tumors. This is concordant with the clinical efficacy observed in certain models by Hong et al., where AZD9150 resulted in tumor reduction in patients who failed prior therapeutic regimens.

While the findings by Hong and co-authors demonstrate the impact of STAT3 inhibition on tumor growth, their promising results with AZD9150 also highlights the potential therapeutic application of ASOs. In earlier studies, the application of methoxyethyl residues (MOEs) and locked nucleic acids (LNAs) proved to enhance the potency of ASOs; however, these additions were linked with increased toxicity when tested in preclinical and clinical settings. Combination of the structural elements of MOEs and LNAs led to the development of constrained MOEs (cMOE) and ethyl residues (cET) (18). Addition of the cMOE or cET modifications to ASOs improved potency and decreased susceptibility to nuclease digestion to a greater degree than the LNA or MOE modifications alone. As shown by Hong et al., AZD9150 displayed greater uptake and potency compared to the second-generation MOE-containing ASOs. The advances made in ASO chemistry can now be exploited for other difficult-to-target genes or driver mutations beyond STAT3. This chemistry can also be applied to the development of oligonucleotide decoy compounds that inhibit protein interaction functions and target specific cells. For example, Zhang et al. have shown that an immune cell-specific STAT3 decoy abrogated leukemia growth and immune checkpoint signaling in a mouse model (19). In this case, the STAT3 decoy was conjugated to a CpG decoy which targets the Toll-like receptor 9 (TLR9) found on immune cells. Their decoy only used phosphorothioate modifications to prevent nuclease digestion. Based on the findings with AZD9150, addition of the cET residues to the CpG-STAT3 decoy may further improve the efficacy and stability of this compound for clinical application.

Taken together, the results by Hong et al. demonstrate the potency of their ASO technology in achieving specific inhibition of STAT3 and the efficacy of their compound in promoting antitumor effects in preclinical and clinical settings. Since the patient cohort used for the dose escalation study was small, further investigations are needed to assess the efficacy and toxicity of AZD9150 in human cancer patients. Additionally, in vitro studies using RNAi molecules have been shown to activate distinct feedback mechanisms from those activated by pharmacological inhibitors (20). Evaluation of the potential feedback mechanisms activated by AZD9150 and similar ASOs also warrants further investigation in light of the promising preliminary findings reported by Hong et al. for AZD9150.

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Footnote

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References


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