IL-17 enhances collagen deposition through HIF1α expression in CAFs. Checkpoint inhibitor therapy (anti–PD-L1) in mice with established tumors activates T cells and increases IL-17 production, leading to increased collagen deposition and inhibition of activated CD8+ T cell access to the tumor, which continues to grow. Deletion of IL-17 receptor on CAFs or blockade of IL-17 induction of HIF1a with an Act1: Hif1a aptamer reduces collagen deposition around the established tumor to allow anti–PD-L1 activated T cells to enter and restrict tumor growth. Figure created with Biorender.com.

demonstrate that rather than inducing *Hif1a* gene expression, IL-17 promotes the translation of HIF1α protein through Act1 binding to *Hif1a* mRNA transcripts. In fact, this is very much on par for IL-17 signaling, which is increasingly found to reinforce and enhance its own signaling outcomes through modulation of RNA-binding proteins including Act1, Arid5a, and Regnase to regulate expression of transcription factors and co-activators (Li et al., 2019).

Antibodies targeting IL-17 and IL-17 receptor are already in clinical use for autoimmune diseases including psoriasis. They have a good safety profile and have been used off-label to reduce autoimmune adverse immune-related events that arise in some patients treated with checkpoint blockade. So, one therapeutic implication of this study would be to incorporate existing IL-17–neutralizing therapies with checkpoint inhibitors, supporting previous studies suggesting this add-on. However, IL-17 blockade does lead to a small increase in the risk of oral infections with *Candida* species and new onset of inflammatory bowel disease in some patients. These side effects correspond to well-established roles for

IL-17 in combating fungal infections in mouse models, particularly oropharyngeal candidiasis, and in maintaining gut health (Majumder and McGeachy, 2021).

The approach employed by Chen et al. (2022) was to more precisely target just one facet of IL-17 signaling by interrupting the binding of Act1 to *Hif1a* mRNA. Aptamers are RNA oligomers designed to mimic the RNA target sequence of an RNA-binding protein, in this case the stem-loop structure that forms the Act1 SEFIR binding element (SBE) on *Hif1a* mRNA transcripts. The aptamer approach was previously employed by this group to target Act1 binding to the SBE at the 3′UTR of IL-17–induced inflammatory mediators *Cxcl1*, *Tnf*, and *Csf2* (Herjan et al., 2018). In that study, Act1 was found to increase the stability of proinflammatory mRNA transcripts downstream of IL-17 signaling, and inflammatory skin disease could be blocked with SBE aptamer. Here, *Hif1a* was found to have a unique SBE that Act1 binds to enhance translation. Excitingly, the *Hif1a*-SBE aptamer did not block inflammatory chemokines and cytokines or metabolic gene expression. It is therefore predicted that the

antimicrobial outcomes of IL-17 signaling and proliferation important for wound healing will be unaffected. Of course, it would be important to confirm this premise in cell type–specific hypoxia assays and fungal infection models if this approach were to move forward to pre-clinical stages.

IL-17 has been associated with fibrotic disease in chronic infection and in idiopathic fibrosis, where anti-inflammatory approaches have not been useful. One could therefore speculate that this aptamer approach to block the pro-fibrotic component of IL-17 signaling could have uses beyond cancer. On the other hand, there are anecdotal reports of impaired wound healing in patients receiving IL-17–blocking biologic therapy for psoriasis, and so aptamers designed to target the inflammatory process while sparing proliferation or matrix production could reduce side effects in autoimmune therapy.

The therapeutic potential raised by the precision approach to targeting RNA-binding protein interactions with specific transcripts is intriguing and vast. Blocking transcription factors such as HIF1α could have broad side effects that reduce their long-term usefulness. However, being able to block a key biological process in a context-dependent way through RNA-binding protein targets suggests a new generation of therapeutics. Act1 is only used by a limited number of receptors, principally IL-17 family cytokines, so the effects should be quite narrowly targeted to IL-17–induced HIF1α induction while sparing HIF1α stabilization when it is induced in a beneficial way by other signals including local hypoxia. The current study highlights the importance of understanding post-transcriptional regulation of gene expression by RNA-binding proteins as an untapped reservoir for therapeutic tuning of immune responses.

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