Development of antitumor immune control strategy by nucleic acid medicine targeting RNA structure

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Abstract

The clinical application of immune-checkpoint blockade therapy has demonstrated that targeting tumor-infiltrating immune cells is effective in cancer patients. However, there are still challenges to be addressed to eradicate cancers completely. Therefore, the development of new therapeutic approaches and strategies is urgently needed.

In the tumor microenvironment, cytotoxic T cell function is suppressed at multiple levels, including through stimulatory and inhibitory receptors, transcription, epigenetic mechanisms, and post-transcriptional mechanisms. Regnase-1, an mRNA decay enzyme, is essential in maintaining immune homeostasis, by suppressing immune cell function post-transcriptionally. Regnase-1 recognizes and degrades stem-loop structures present in the 3' untranslated region of target genes such as inflammatory cytokines. Since Regnase-1 deficiency causes hyperactivation of T cells, characterized by their increased proliferative activity and capacity to produce effector molecules, such as IFN-γ, there has been increasing attention paid to cancer immunotherapy targeting Regnase-1. Although it has been thought that Regnase-1 regulates T cell functions by targeting multiple mRNAs, we discovered Nfkbiz as a key target for T cell activation by analyzing Regnase-1-deficient mice. Furthermore, we developed a nucleic acid-based therapeutic approach to enhance T cell cytotoxic function.

In this poster session, we would like to introduce our strategy for enhancing cancer immunity using nucleic acid therapeutics and discuss its effectiveness.