Targeting CISH enhances natural cytotoxicity receptor signaling and reduces NK cell exhaustion to improve solid tumor immunity


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**In brief:**
Targeting CISH improves NK cells ex-vivo proliferation, functions and signaling activation of several pathways such as cytokines and NK activating receptors. In vivo CISH absence favors NK cells infiltration to the tumor burden, optimize their killing properties and limits NK cells exhaustion. Consequently, primary tumor and metastasis development are greatly impaired in pre-clinical mouse model. Finally, we targeted CISH in human NK-92 or primary NK cells, using a technology combining the CRISPR(i)-dCas9 tool with a new lentiviral pseudotype, this, improving their function. Our results validate CISH as an emerging therapeutic target to enhance NK cell immunotherapy.