1009 CO-STIMULATORY SIGNALS VIA CD28 AND CD27 COLLABORATE TO REGULATE ACTIVATION AND IL-2 PRODUCTION OF CD8$^+$ T CELLS THROUGH DISTINCT MECHANISMS

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Background CD8$^+$ T cells play a central role in immune protection against infectious and malignant disease, and their activation and differentiation are regulated by the spatio-temporal engagement of co-stimulatory and inhibitory receptors. These receptors constitute key targets for the therapeutic modulation of T cell responses, as evidenced by the clinical success of immune checkpoint inhibitors (ICI) in some cancer patients. Strategies aiming improve the efficacy and breadth of ICI therapy include the combination with agonistic targeting of co-stimulatory receptors. However, it remains incompletely understood how different co-stimulatory pathways interact to induce efficacious T cell responses.

Methods and Results By interrogating the co-stimulatory requirements for effective CD8$^+$ T cell activation using kinase activity profiling, we found that engagement of the co-stimulatory receptors CD27 and CD28, individually or in combination, had differential impacts on intracellular signaling pathways. Moreover, CD27-CD70 and CD28-CD80/86 co-stimulatory pathways differentially impacted the transcriptional program of CD8$^+$ T cells following T cell receptor engagement, including *Il2* expression. Importantly, signaling via CD27 and CD28 distinctly contributed to *de novo* transcription and post-transcriptional regulation of *Il2* mRNA, respectively. Expression and nuclear translocation of the transcription factor c-Rel, a NF-kB family member critical for IL-2 transcription, was differently regulated by CD27- and CD28-mediated co-stimulatory signals, with full induction requiring collective signaling. Using co-stimulation-deficient systems, we found that cytokine production, particularly IL-2 secretion, by virus-specific CD8$^+$ T cells was collectively dependent on both the CD27-CD70 and CD28-CD80/86 co-stimulatory pathways. This co-stimulation-dependent effect on the quality of antigen-specific CD8$^+$ T cells was programmed early after viral infection, and persisted long-term. In line with the autocrine role of IL-2, deficient co-stimulation via CD27 and CD28 severely impaired T cell expansion during primary and memory responses, which could be partially rescued by constitutive IL-2 expression.

Conclusions Collectively, our results demonstrate that the CD27-CD70 and CD28-CD80/86 co-stimulatory pathways act in a distinct, yet collaborative manner to instruct effective cytokine and proliferative responses of CD8$^+$ T cells. These findings may inform the conception and development of immunotherapies harnessing the protective capacity of CD8$^+$ T cells, including novel vaccine strategies, agonistic targeting of co-stimulatory receptors, and adoptive cell therapies.

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