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STEM CELLS

Escape from the Jedi

Adult stem cells are long-lived, undifferentiated cells that are crucial for tissue maintenance and repair. These cells can be the target of immune surveillance, for example during immune rejection of transplanted tissues, or because they express neoantigens as a result of an increased mutational burden owing to their longevity, or potentially during immunotherapy when one of the immune system's brakes is removed. Agudo *et al*. now report that quiescent stem cells escape immune surveillance, whereas more proliferative stem cells do not, a difference that is related to whether they express the antigen presentation machinery.

The authors used Jedi (just EGFP death-inducing) T cells, which express a T cell receptor specific for a peptide derived from enhanced green fluorescent protein (EGFP), to selectively target stem cells in mice expressing GFP from the promoter of the stem cell marker *Lgr5* (LGR5-GFP mice). The researchers injected LGR5-GFP mice with Jedi T cells or control T cells as well as GFP (to activate the Jedi T cells), and examined LGR5$^+$ stem cells in various tissues after one week. The LGR5$^+$ stem cell population was depleted in tissues containing actively dividing stem cells, such as the gut, the ovaries and the mammary glands. Surprisingly, stem cells were not depleted in tissues with a less actively dividing stem cell population, such as the hair follicle and muscle. Additionally, even in the hair follicle, stem cell survival was dependent on the stage of the hair growth cycle, as only LGR5$^+$ stem cells in the anagen (growing) stage, but not those in the telogen (resting) stage, were eliminated by Jedi T cells.

The resistance to T cell-mediated killing was cell-autonomous, as the quiescent LGR5$^+$ stem cells still escaped killing by Jedi T cells in *ex vivo* co-cultures. The authors examined the expression of MHC class I, and found that it was downregulated in both quiescent hair follicle stem cells and muscle stem cells. RNA sequencing analysis revealed that multiple genes involved in antigen presentation were downregulated in stem cells from hair follicles in telogen compared with those in anagen, and these genes contained regulatory motifs for NLR family CARD domain-containing protein 5 (NLRC5). Perhaps not surprisingly, *Nlrc5* expression was almost undetectable in LGR5$^+$ stem cells from telogen hair follicles, whereas it was readily detectable in proliferating stem cells from anagen hair follicles, suggesting that differences in NLRC5 activity (and thus antigen presentation) may explain the differing susceptibility of quiescent and proliferating stem cells to T cell targeting.

As cells expressing low or undetectable levels of MHC class I are usually targeted and killed by natural killer (NK) cells, the researchers confirmed that quiescent stem cells escaped this fate. Therefore, quiescent stem cells seem to have adaptations that enable them to avoid detection by both cytotoxic T cells and NK cells. However, the mechanism of this avoidance of NK cell-mediated killing, as well as how *Nlrc5* levels are regulated in stem cells with different proliferative capacities, awaits further study.

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