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REGULATORY T CELLS

Muscling in on repair

Regulatory T (T_{Reg}) cells are best known for their role in controlling other immune cells but recent studies have described a regulatory role for distinct populations of T_{Reg} cells in non-immunological processes. Reporting in *Cell*, Mathis and colleagues describe the discovery of 'muscle T_{Reg} cells', which are phenotypically and functionally distinct T_{Reg} cells that promote muscle repair.

Intramuscular injection of cardiotoxin, which induces rapid myofibre necrosis, is a well-studied mouse model of muscle tissue repair after acute injury. In this model, myeloid mononuclear cells with a pro-inflammatory phenotype rapidly accumulate after injury but this population switches to an anti-inflammatory phenotype with pro-regenerative functions by day 4. T cells also accumulate in the injured muscle. The authors found that the phenotypic switch in the myeloid mononuclear cell population was accompanied by an accumulation of forkhead box protein P3 $(FOXP3)^+$ T_{Reg} cells, and by day 14 post injury ~50% of the $CD4^+$ T cells in the injured muscle expressed FOXP3.

A comparison of the transcriptome of T_{Reg} cells from the injured muscle, from adipose tissue and from lymphoid organs showed that muscle T_{Reg} cells were most similar to (but still distinguishable from) adipose tissue T_{Reg} cells and were distinct from lymphoid organ T_{Reg} cells. Furthermore, 20–40% of the muscle T_{Reg} cell population had undergone clonal expansion (there was no evidence of clonal expansion in T_{Reg} cells from lymphoid organs) and had a unique T cell receptor repertoire. These data indicate that T_{Reg} cells in acutely injured muscle undergoing repair are a unique population, probably responding to an antigen.

Notably, T_{Reg} cell depletion at the time of cardiotoxin administration had marked effects on the muscle repair process. First, the size of the cellular infiltrate was increased (including an increase in the frequency of conventional T cells) and the myeloid mononuclear cell population did not undergo the expected phenotypic switch. Second, the histological features of skeletal muscle repair were altered, with a reduced number of regenerative myofibres, a disorganized tissue structure and an accumulation of collagen. Third, satellite cells, which are the main source of regenerative myofibres in acutely injured muscle, had decreased colony-forming capacity. Fourth, the expression of groups of genes encoding proteins with important roles in muscle homeostasis and in muscle repair was disrupted in whole-muscle tissue. Together, these data show that T_{Reg} cells have an important role in muscle repair following acute injury.

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The authors showed that muscle T_{Reg} cells produce the growth factor amphiregulin. The fraction of muscle T_{Reg} cells expressing amphiregulin started to increase on day 4 and peaked on day 7 following cardiotoxin administration. Of note, intramuscular administration of amphiregulin to cardiotoxin-treated T_{Reg} cell-depleted mice normalized the expression profile of the gene groups associated with muscle homeostasis and repair. In addition, amphiregulin enhanced the colony-forming capacity of satellite cells from wild-type mice.

This study identifies a unique population of T_{Reg} cells that accumulates at sites of acute muscle injury and potentiates wound healing and repair. Furthermore, in two different mouse models of muscular dystrophy, the authors showed that T_{Reg} cells also have a reparative role in chronic muscle injury.

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> “T_{Reg} cell depletion … had marked effects on the muscle repair process”

ORIGINAL RESEARCH PAPER Burzyn, D. *et al.* A special population of regulatory T cells potentiates muscle repair. *Cell* **155**, 1282–1295 (2013)