Nature Reviews Immunology | Published online 25 Nov 2016; doi:10.1038/nri.2016.133

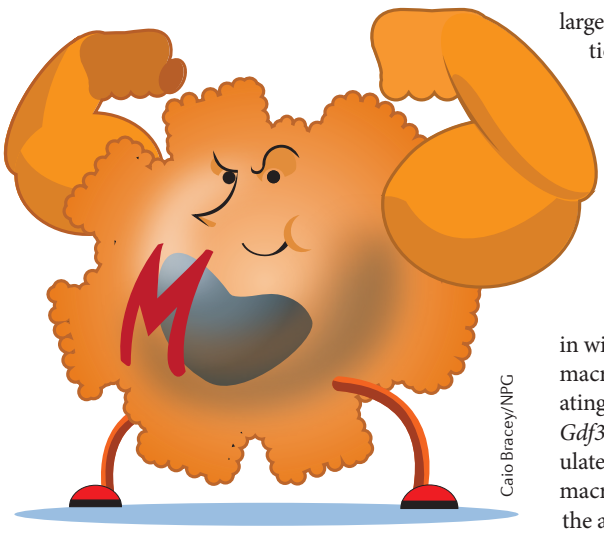
MACROPHAGES

Macrophage muscle man

> PPARγ-dependent soluble factors might regulate muscle regeneration

Immune cells, in particular macrophages, support the regeneration of injured tissues. But how macrophages sense and remove the damaged tissue, then initiate the repair process is not fully understood. Recent research published in *Immunity* indicates that the lipid-activated transcription factor PPARγ (peroxisome proliferator-activated receptor-γ) is required in repair macrophages during skeletal muscle regeneration. It acts as a metabolic sensor and transcriptional regulator leading to the secretion of growth differentiation factor 3 (GDF3), which promotes muscle regeneration.

The authors identified a role for PPARγ-expressing macrophages in skeletal muscle regeneration using a model of injury caused by intramuscular injection of the snake venom cardiotoxin. Analysis of gene expression profiles of macrophages infiltrating injured muscle revealed high expression of *Pparg*. Mice with a specific deletion of *Pparg* in myeloid lineages showed a pronounced delay in muscle regeneration following toxin-induced injury compared with wild-type animals. In particular, the area of regenerating muscle fibres was smaller, there was a greater number of phagocytic or necrotic fibres and inflammatory infiltrates persisted. The findings were confirmed using bone marrow chimeric mice: animals reconstituted with PPARγ-deficient bone marrow exhibited a profound deficit in muscle regeneration.



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The authors then investigated why macrophage PPARγ deficiency leads to impaired muscle regeneration. They found it was not due to decreased macrophage infiltration or phagocytosis activity but it seemed to be caused by a poorer ability to promote muscle differentiation. *In vitro* assays showed that conditioned medium from interleukin-4 (IL-4)-treated wild-type bone marrow-derived macrophages promoted a large increase in myoblast differentiation, and this was abrogated when conditioned medium from IL-4-treated PPARγ-deficient macrophages was used in the cultures of differentiating myoblasts. This suggests that PPARγ-dependent soluble factors might regulate muscle regeneration.

Comparison of gene expression in wild-type and PPARγ-deficient macrophages isolated from regenerating muscle highlighted one gene, *Gdf3*, that was consistently downregulated in all PPARγ-deficient muscle macrophage subsets. Accordingly, the authors identified several PPARγ-binding active enhancers near the *Gdf3* transcriptional start site. *Gdf3* seemed a likely candidate for mediating muscle regeneration because it encodes a secreted factor and is a member of the transforming growth factor-β family, which includes known regulators of muscle regeneration.

Consistent with a role in muscle regeneration, GDF3 protein expression peaked at day 4 following muscle injury, at a time when inflammation subsides and regenerative processes start to dominate. Importantly, bone marrow-ablated mice reconstituted with GDF3-deficient bone marrow showed impaired muscle regeneration after toxin-induced injury that was comparable to defects in mice reconstituted with PPARγ-deficient bone marrow. Moreover, injection of recombinant GDF3 into toxin-injured muscles rescued the regeneration defect of mice with conditional PPARγ deficiency. *In vitro* studies confirmed that GDF3 was a potent inducer of myotube formation, signalling through a SMAD2 pathway to promote the expression of genes known to be involved in myoblast fusion and muscle regeneration.

So, the PPARγ–GDF3 axis acts as a sensory-regulatory-effector mechanism by which macrophages regulate the regenerative potential of myogenic precursor cells.

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ORIGINAL ARTICLE Varga, T. *et al.* Macrophage PPARγ, a lipid activated transcription factor controls the growth factor GDF3 and skeletal muscle regeneration. *Immunity* http://dx.doi.org/10.1016/j.immuni.2016.10.016 (2016)