<Further Development 24_11>

Immune Cells to the Regeneration!

If you have ever been injured and felt the swelling around the affected area and experienced the scar that develops over time, you are well aware that there is an elaborate immune response immediately following an injury. Is the immune system at all connected to the initiation and process of regeneration? A recent study in zebrafish has demonstrated that a subtype of T cells called regulatory T cells (T_{reg} cells) seems to rapidly invade injured tissues, including the eye, spinal cord, and heart (Hui et al. 2017). Targeted loss of T_{reg} cells in the adult zebrafish prevents regeneration in each of these different organ systems (Figure 1). Most interesting is that these T_{reg} cells recognize the type of tissue injured and respond by upregulating specific growth factors that promote a specific pro-regenerative response in these tissues. For instance, T_{reg} cells in the heart upregulate *neuregulin-1*, which is capable of inducing cardiomyocyte proliferation even when T_{reg} cells are depleted (Figure 2). This is a remarkable study that demonstrates a clear emergency response from the immune system that appears to provide tailored pro-regenerative care for the specific tissue type injured. Whether this ability is conserved across highly regenerative species remains to be seen. It is nonetheless enticing to explore whether T_{reg} cells and the therapies they provide could be leveraged to enhance pro-regenerative instead of scarring responses in us.

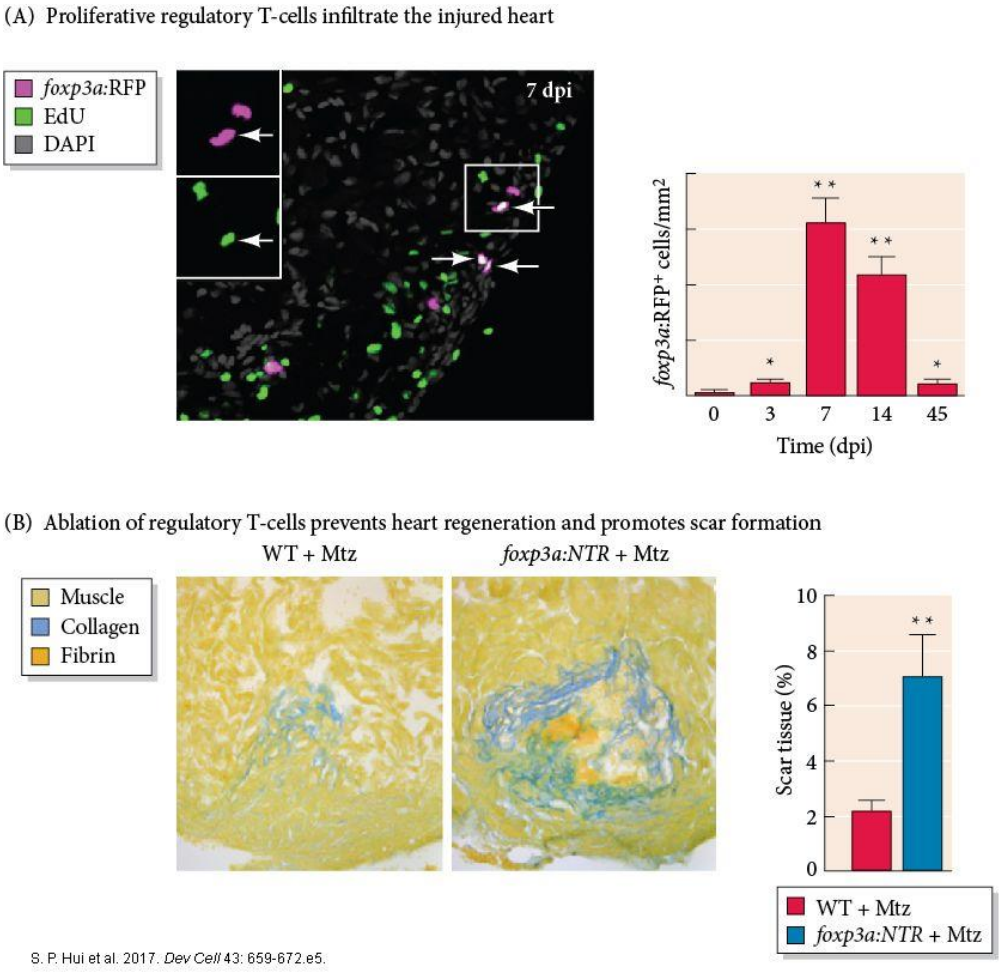
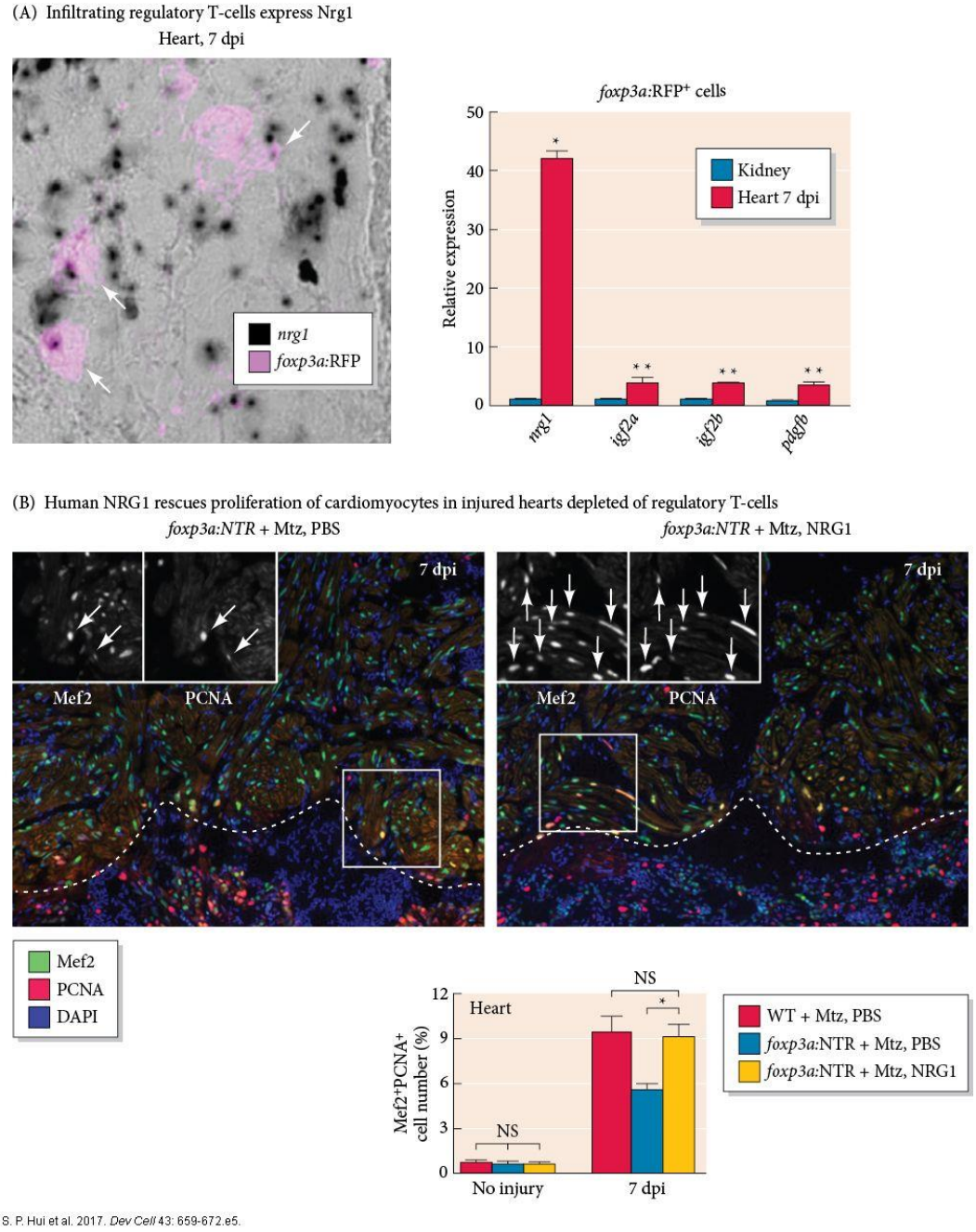


Figure 1 Regulatory T cells are required for heart regeneration in zebrafish. (A) *Tg*(*foxp3a:RFP*) transgenic zebrafish reporter enables the observation of an infiltration response by regulatory T cells to a heart injury. Dpi, days post-injury.

Boxed area is shown in magnified insets with double labeled cells noted (arrows). The increasing number of T cells was quantified over time (graph to right). (B) Treatment with the prodrug metronidazole (Mtz) is harmless to fish unless they are genetically engineered to express the enzyme nitroreductase (NTR), which converts Mtz into a cytotoxin, triggering cell death. Treating *Tg*(*foxp3a:NTR*) transgenic fish with Mtz specifically ablates regulatory T cells, which if done following heart ablation halts the zebrafish's ability to regenerate, and instead promotes fibrotic scar formation, as indicated by the excessive collagen (blue) and fibrin (orange) that was quantified (graph to right). *p < 0.01, **p < 0.01, Mann-Whitney U test.



S. P. Hui et al. 2017. *Dev Cell* 43: 659-672.e5.

Figure 2 Neuregulin-1 (Nrg1) is sufficient to compensate for the loss of regulatory T cells by stimulating cardiomyocyte proliferation in the regenerating zebrafish heart. (A) Infiltrating regulatory T cells upregulate *neuregulin-1* (*nrg1*) expression during heart regeneration. Graph to right shows genes upregulated in T cells from regenerating heart in comparison to T cells from other tissues. (B) Administration of recombinant human NRG1 protein induces cardiomyocyte proliferation even in the absence of regulatory T cells (Mtz treated *Tg*(*foxp3a:NTR*) transgenic fish) as quantified in graph to right. PCNA, proliferating cell nuclear antigen. *p < 0.05, **p < 0.01, Mann-Whitney U test.

Literature Cited

Hui, S. P., D.Z. Sheng, K. Sugimoto, A. Gonzalez-Rajal, S. Nakagawa, D. Hesselson, K. Kikuchi. 2017. Zebrafish Regulatory T Cells Mediate Organ-Specific Regenerative Programs. *Dev Cell* 43(6):659-672.e5.
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