182. Method to inhibit neutrophil recruitment to damaged tissue

(Wisconsin Alumni Research Foundation)

Asset Overview

Product Type	Protein
Disease Area	Inflammatory Disease
Indication	Autoimmune Disorders
Current Stage	Lead Optimization
Target	The HIF-1a pathway
MoA	Myeloid-derived growth factor (MYDGF) is a damage signal that regulates neutrophil interstitial motility and inflammation through a HIF-1a pathway in response to tissue damage.
Brief Description	• Myeloid-derived growth factor (MYDGF) is known to mediate cardiac repair following myocardial infarction by inhibiting cardiac myocyte apoptosis. MYDGF (C19orf10) mediates cardiac repair following myocardial infarction. MYDGF-deficient mice developed larger infarct scars and more severe contractile dysfunction compared to wild-type mice. Treating the mice with recombinant MYDGF reduced scar size and contractile dysfunction after myocardial infarction. • A method to inhibit neutrophil recruitment to damaged tissue in a subject , the method comprising administering to a subject, the subject having a wound and/or a burn at a site on the subject, an amount of a MYDGF, a biologically active fragment thereof, an analogous sequence thereof , or a pharmaceutically suitable salt of any of the foregoing, wherein the amount is effective to inhibit neutrophil recruitment to the wound and/or burn site. • A method to inhibit inflammation in a subject, the method comprising administering to the subject an anti-inflammatory-effective amount of a MYDGF, a biologically active fragment thereof , an analogous sequence thereof, or a pharmaceutically suitable salt of any of the foregoing.
Intellectual Property	US20220168390A1
Publication	Myeloid-derived growth factor regulates neutrophil motility in interstitial tissue damage. J Cell Biol, (2021)
Inventors	Anna Huttenlocher, Deane Mosher, Valeriu Bortnov, David Bennin

Highlights

- MYDGF regulates neutrophil responses to tissue damage, but not infection.
- MYDGF depletion leads to a neutrophil-dependent defect in wound healing.
- MYDGF depletion alters neutrophil motility in the wound microenvironment.
- MYDGF depletion impairs neutrophil reverse migration and resolution following injury.
- Neutrophil accumulation in the mydgf mutant is dependent on the HIF-1α pathway.

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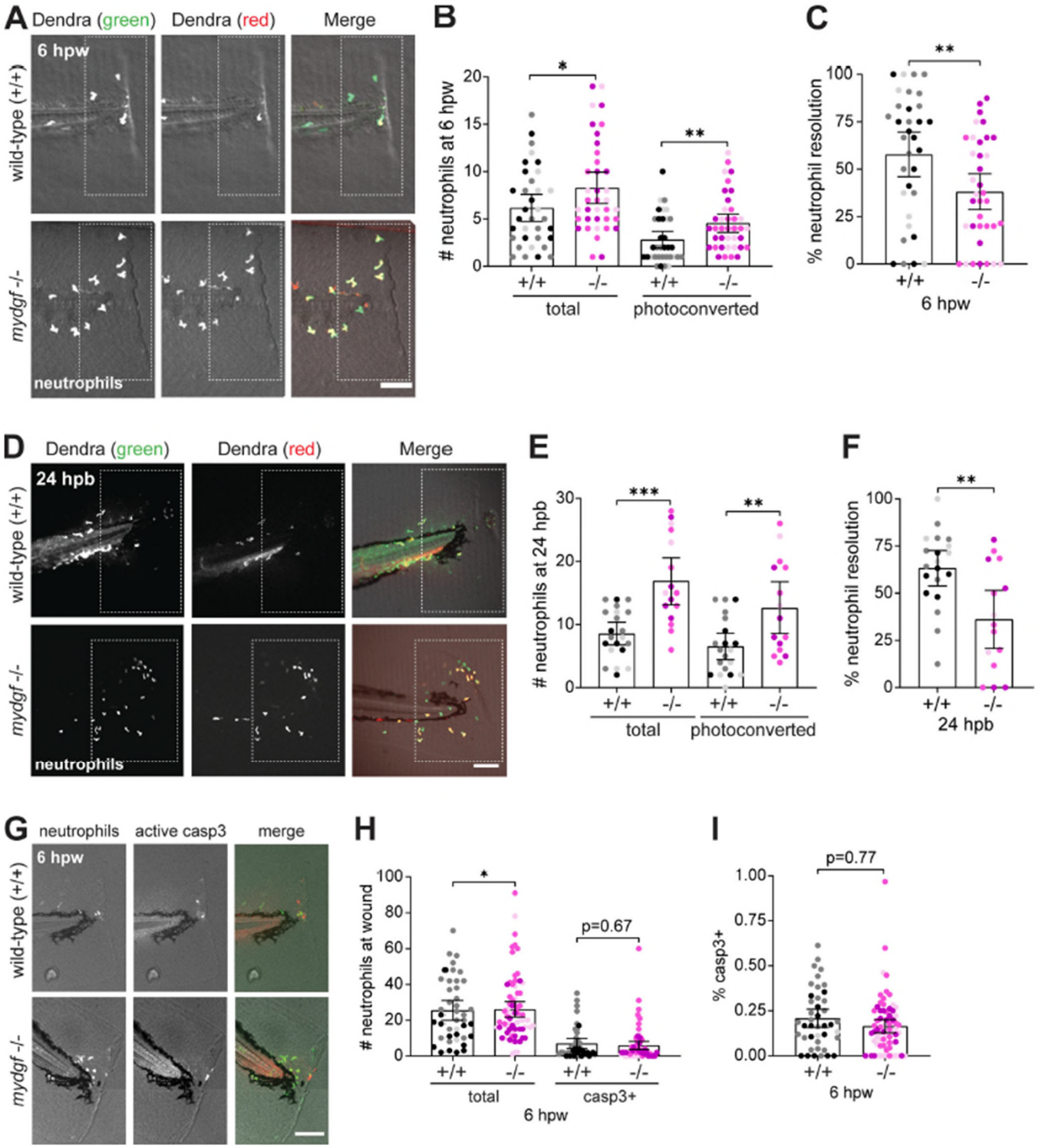
Key Data

MYDGF depletion impairs neutrophil reverse migration and resolution following injury.



To be continued

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MYDGF depletion impairs neutrophil reverse migration and resolution following injury.

(A and B) Representative images (A) and quantification (B) of green (total) and red(photoconverted) dendra2-labeled neutrophils in the wound microenvironment at 6 hpw following tail transection of 3 dpf WT and mydgf−/− larvae; three independent replicates with n = 33 +/+ and 36 −/−; scale bar = 100 μm.
(C) Quantification of the percentage of photoconverted neutrophils present at the wound at 2 hpw that are no longer present at 6 hpw in the same larva.
(D and E) Representative images (D) and quantification (E) of green (total) and red (photoconverted) dendra2-labeled neutrophils in the burn at 24 hpb following thermal injury of the caudal fin of 3 dpf WT and mydgf−/−larvae; three independent replicates with n = 20 +/+ and 15 −/−; scale bar = 100 μm.
(F) Quantification of the percentage of photoconverted neutrophils present in the burn microenvironment at 3 hpb that are no longer present at 24 hpb in the same larva.
(G) Representative images of immunostaining for active caspase-3 (casp3) following tail transection of 3 dpfWT and mydgf−/− larvae withmCherry-labeled neutrophils at 6 hpw; scale bar = 100 μm.
(H) Quantification of total and active caspase-3–expressing neutrophils in the wound at 6 hpw; three independent replicates with n = 42 +/+ and 71 −/−.
(I) Proportion of neutrophils in the wound expressing active caspase-3 at 6 hpw. In B, C, E, F, H, and I, data are expressed as mean with 95% CI; each symbol represents one larva, and different colors represent the results of three independent replicates. *, P < 0.05; **, P < 0.01; ***, P < 0.001. P values were calculated by ANOVA with Tukey's multiple comparisons.

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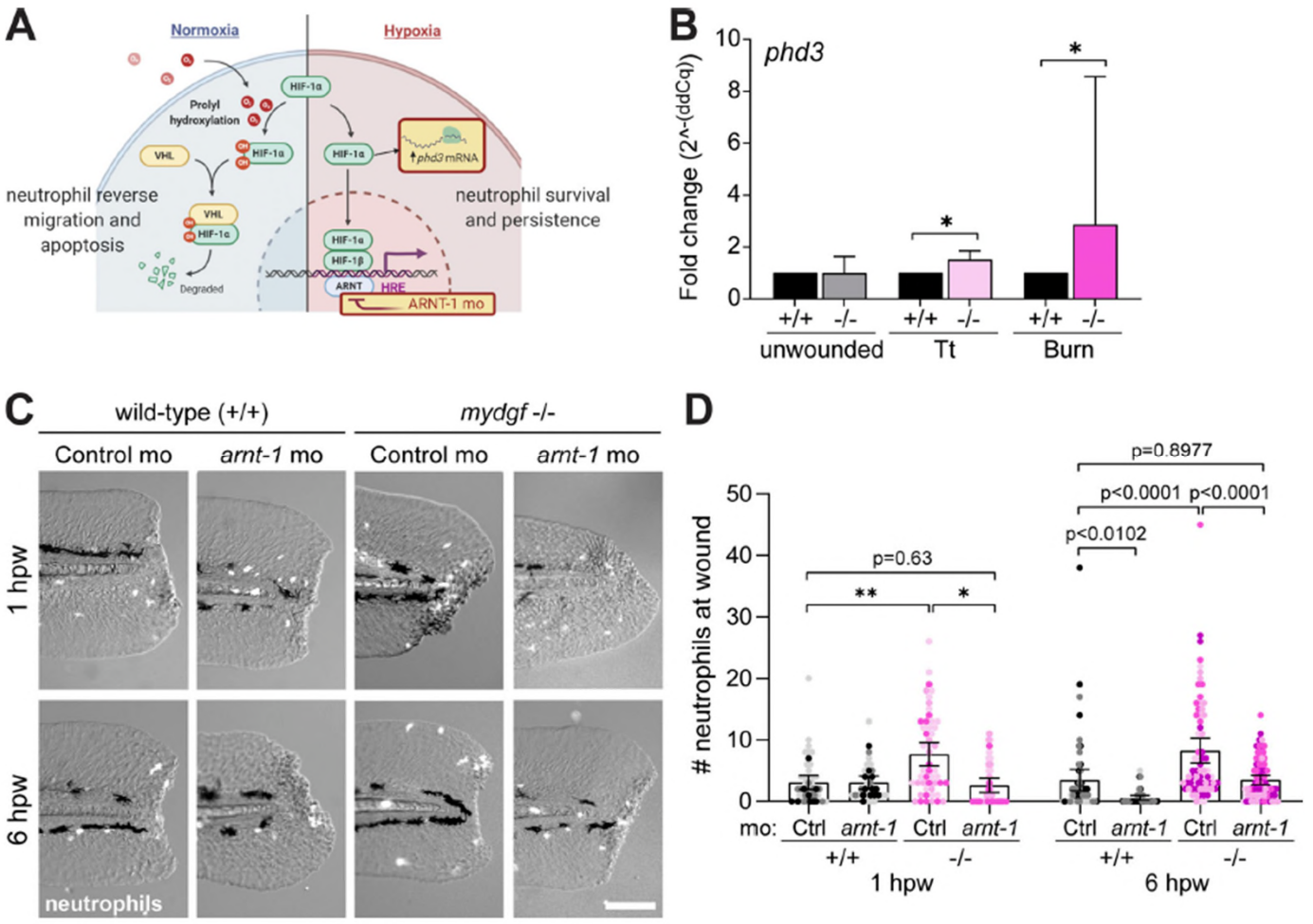
Neutrophil accumulation in the mydgf mutant is dependent on the HIF-1α pathway.



(A) Schematic representation of HIF-1α activation in neutrophils. Pathway activation results in neutrophil persistence and survival and is characterizeed by increased expression of phd3. HIF-1α pathway activation can be blocked at the level of transcription factor nuclear binding using arnt-1 morpholino. Illustration was created at www.biorender.com. (B) phd3 expression in pooled tail fin tissue collect from WT larvae, either unwounded or 3 h following tail transection (Tt) or thermal injury (burn), measured by RT-qPCR. Data comprise three (burn) to five (Tt) independent replicates performed in technical triplicates and normalized to mydgf expression in unwounded tails and to ef1α. n = 50 tails per condition per independent replicate. *, $P < 0.05$. Fold changes in gene expression were compared with the normalized value of 1 using one-sample t tests. (C and D) Representative images (C) and quantification (D) of the number of mCherry-labeled neutrophils at the wound inWT and mydgf−/−larvae, with control or arnt-1 morpholino, at 1 and 6 hpw after Tt; three or four independent replicates with n = 46 +/+ control mo, 33 +/+ arnt-1 mo, 50 −/− control mo, and 38 −/− arnt-1 mo at 1 hpw and 54 +/+ control mo, 38 +/+ arnt-1 mo, 68 −/− control mo, and 73 −/− arnt-1 mo at 6 hpw; scale bar = 100 μm.
Data are expressed as mean with 95% CI; each symbol represents one larva, and different colors represent independent replicates. *, $P < 0.05$; **, $P < 0.01$. P values were calculated by ANOVA with Tukey's multiple comparisons.