Two related extracellular proteins Kret and Ogon are required for zebrafish fin regeneration

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Zebrafish (Danio rerio) is a teleost fish, common in home aquarium. This animal has emerged as a powerful model organism for studies of vertebrate development, diseases, biological pathways, toxicology mechanisms and organ regeneration. The adult teleost fish has the capacity to regenerate several organs, including their appendages, optic nerve, heart, spinal cord. These organs display poor regenerative potential in mammals.

In this study, we investigate molecular mechanisms of fin regeneration. This process depends on creation of blastemal progenitor cells located underneath the wound epidermis. Using microarray analysis, we identified two novel homologous genes, kret and ogon, which are transcriptionally upregulated during fin regeneration. First, we confirmed this finding by qRT-PCR analysis that revealed more than a hundredfold increase of kret and ogon expression levels in regenerating fins as compared with the uninjured control fins. The expression analyses by in situ hybridization demonstrated the localization of kret mRNA in the basal layer of the wound epidermis and in the blastema, which are the key structures required for appendage regeneration. ogon mRNA was detected in the blastema, but not in the wound epidermis. Using specific antibodies against both proteins, we showed that both Kret and Ogon are colocalized in the blastema and build highly organized extracellular tubular network, which has not been previously visualized in regenerating fins. We investigated the regulation of Kret and Ogon expression by blocking several signaling pathways, such TGFβ, IGF and FGF, which have been shown to be required for blastema formation. We found that the expression of kret was strongly decreased, when these pathways were inhibited upon fin injury and the fin regeneration was blocked. Finally, we performed functional studies of Kret and Ogon by the knockdown morpholinos technology. The knockdown of either of the genes resulted in impaired outgrowth formation. We concluded that the blastemal tubular network of Kret and Ogon is required for fin regeneration in zebrafish.

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