Early TGFb Signaling is Required for Tail and Spinal Cord Regeneration in the Mexican axolotl (Ambystoma mexicanum)

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TGF-β signaling is required for many regenerative processes in vertebrates, including salamander limb, frog tail, and fish fin regeneration. Here, we investigated the requirement of Tgf-β signaling on tail and spinal cord regeneration using Mexican axolotl (Ambystoma mexicanum) embryos and chemical inhibitors of Smad and non-Smad signaling pathways (SB505124 and Naringenin). Both SB505124 and Naringenin completely blocked tail and spinal cord regeneration and reduced levels of phospo-Smad2 (pSmad2) and pSmad3 as early as 1-hour post amputation (1hpa). However, more complex changes in pErk and pAkt were observed between the chemical treatments. At 1hpa, levels of pErk and pAkt were significantly higher in SB505124-treated embryos, but significantly lower in Naringenin-treated embryos. At 6hpa and 12hpa, SB505124 significantly affected levels of pErk while Naringenin significantly affected levels of pAkt. The differential effects of SB505124 and Naringenin on non-Smad signaling pathways was associated with transcriptional differences at 12 and 24 hpa, with many non-overlapping target genes identified among SB505124, Naringenin, and SB505124 / Naringenin co-treated embryos. Our results show that TGF-β signaling via Smad and non-Smad signaling pathways are activated very early after axolotl tail amputation to regulate transcriptional changes that associate with tail and spinal cord regeneration. Overall, our study enriches understanding of signaling network dynamics that underlie tissue regeneration.