Optimal Combinations of Transcription Factors for CNS Axon Regeneration

December 11

Tuesday, 12:30 pm

Weekly Colloquium

Billings Building
Rosedale Conference Room

Speaker: Murray Blackmore, Ph.D.
Associate Professor,
Department of Biomedical Sciences,
College of Health Sciences
Marquette University

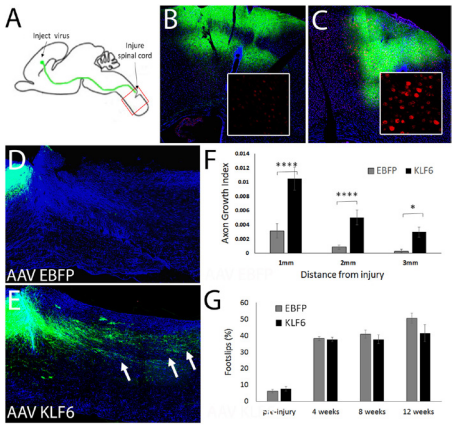
Host: Edmund R. Hollis II, Ph.D.

For more information, please contact
Darlene White at
daw9085@med.cornell.edu

Burke Neurological Institute
Academic Affiliate of Weill Cornell Medicine
785 Mamaroneck Avenue
White Plains, NY 10605
burke.weill.cornell.edu

Abstract

Axon regeneration in the central nervous system (CNS) is limited in part by the failure of injured neurons to initiate intrinsic cellular programs that support axon growth. One promising strategy to improve axon growth is to force the expression of pro-regenerative transcription factors (TFs) in injured neurons. For example, viral delivery of TFs including Sox11, KLF7, or KLF6 to corticospinal tract neurons can enhance regenerative growth after spinal injury. However, even with TF treatments the overall number and regenerative speed of axons remains insufficient for full functional recovery. TFs rarely function in isolation, and thus a core challenge is to identify combinations of interacting TFs that can restore regenerative potential more completely. To do so we have focused on the concept of TF co-occupancy, in which synergy between TFs results from the binding of multiple TFs to common promoters and/or enhancers. Importantly, co-occupancy produces functional synergy in the absence of direct physical interaction between TFs and is missed in analyses that depend on protein-protein interactions. An emerging technique called ATAC-seq footprinting now enables unprecedented information about patterns of TF binding across the genome. We examined the developing cortex across ages that span the loss of regenerative ability, using ATAC-seq footprinting to identify clusters of TFs that co-occupy regulatory DNA in networks of genes with pro-growth functions. To functionally test the candidate TF clusters, we systematically co-expressed TFs in assays of neurite outgrowth in post-natal CNS neurons, and found multiple instances of functional synergy. Network modeling of the top hits from this combinatorial screen indicated a central core of factors with maximal interactions: KLF6, STAT3, EOMES, RARB, NR5A2, and NKX3.2. Remarkably, an independent bioinformatic pipeline built on RNA-seq analysis of KLF6 target genes also converged on this same set of core factors, raising confidence in their relevance. In ongoing experiments, we are using Retro-AAV vectors to deliver selected sets of factors to corticospinal neurons in mouse models of spinal injury in order to test for synergistic gains in axon growth. Overall we expect this research to identify novel transcriptional networks that can be manipulated to increase axon regeneration following CNS injury.



1. Jayaprakash N, Wang Z, Hoeynck B, Krueger N, Kramer A, Balle E, Wheeler DS, Wheeler RA, Blackmore MG (2016) Optogenetic Interrogation of Functional Synapse Formation by Corticospinal Tract Axons in the Injured Spinal Cord. J Neurosci 36:5877–90.
2. Venkatesh I, Mehra V, Wang Z, Califf B, Blackmore MG (2018) Developmental chromatin restriction of pro-growth gene networks acts as an epigenetic barrier to axon regeneration in cortical neurons. Dev Neurobiol 78(10):960-97.
3. Wang Z, Maunze B, Wang Y, Tsoulfas P, Blackmore MG (2018) Global connectivity and function of descending spinal input revealed by 3D microscopy and retrograde transduction. J Neurosci1196-18

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