SCHOOL OF MEDICINE & DENTISTRY
UNIVERSITY of ROCHESTER

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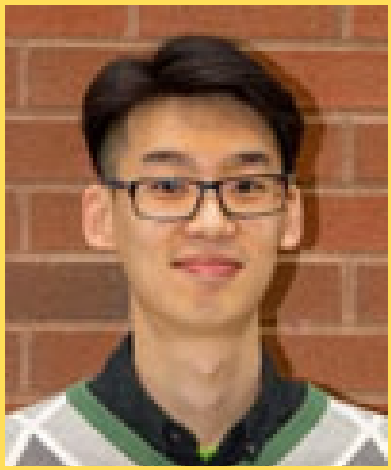
Presents:
In a PhD Thesis Defense
Advisor: Mark Noble

Neuroscience Graduate Program



Yunpeng Pang

Redox-Fyn-c-Cbl (RFC) pathway regulates O-2A/OPC cell cycle exit and differentiation by thyroid hormone and negative regulation of the RFC pathway during early OPC development

Thyroid hormone (TH) plays an important role in the development of the central nervous system (CNS). In particular, TH signal is critical for the differentiation of oligodendrocyte precursor cells (O-2A/OPCs) into oligodendrocytes, which myelinate the CNS. Although gene regulations by TH and TH receptors have been the focus of the field, it is still not clear how does TH drive cell cycle exit in dividing OPCs. Previous work from the Noble laboratory revealed that intracellular redox status is a central regulator of OPC fate decisions between cell division and differentiation. Here, we report the critical role of c-Cbl, a tumor suppressor protein, in regulating the cell cycle exit of dividing OPCs in response to TH signal via the redox-Fyn-c-Cbl (RFC) pathway. In particular, we found that treatment of TH in vitro leads to increased intracellular reactive oxygen species (ROS) production and superactivation of c-Cbl, downregulation of multiple targets of c-Cbl including PDGFRa, and subsequently leading to OPC cell cycle exit. We found that c-Cbl is required for TH-driven downregulation of multiple c-Cbl targets and cell cycle proteins, as well as OPC cell cycle exit. Additionally, we found that other glial differentiation signals including TGF-β and BMP4 converge on the activation of the RFC pathway and that they similarly require generation of ROS to drive OPC cell cycle exit. We also found that in vivo injection of TH in a hypothyroid model resulted in c-Cbl superactivation and led to downregulating of c-Cbl target PDGFRa, suggesting that activation of the RFC pathway is relevant in an in vivo setting.

The RFC pathway is also carefully regulated during early development and we uncovered two mechanisms by which c-Cbl superactivation can be dampened to allow proliferation of OPCs during development despite oxidation and ROS signaling by prodifferentation factors. First, growth factors such as NT3 decreased the ability of ROS generation by TH. Secondly, we found that bioactive lipid sphingosine-1 phosphate (S1P) induced inhibitory complex formation between c-Cbl and β-pix. Intriguingly, in early embryonic human fetal derived OPCs we found the inhibitory complex between c-Cbl and beta-pix exist and prevented TH induced c-Cbl superactivation and cell cycle exit by TH. Here, we investigated whether the c-Cbl/β-pix inhibitory complex is required for embryonic human OPCs to resist TH-induced c-Cbl superactivation and found that both pharmacological inhibition of upstream regulators of β-pix and genetic knockdown of β-pix itself released the negative control of c-Cbl superactivation and allowed embryonic human OPCs to response to TH, leading to cell cycle exit and accelerated of OL generation. Our findings provide a novel molecular architecture of c-Cbl superactivation via the RFC pathway as well as negative regulation of c-Cbl superactivation. Together these mechanisms help to shed light on the potentially critical role of c-Cbl in the development of glial progenitors in the CNS.

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