2019 CCUBC Graduate Student Research Prize
Dr. Navroop Dhaliwal
University of Toronto, Toronto, ON

KLF4 protein stability regulated by interaction with pluripotency transcription factors overrides transcriptional control (PDF)

Dr. Jennifer Mitchell nomination letter in support of Dr. Navroop Dhaliwal (PDF)

Dr. Navroop Dhaliwal joined Mitchell lab Department of cell and systems biology, University of Toronto in 2011 after completing her M.S from University pf New Haven to continue her graduate studies as a doctoral student. Her PhD research investigated the earliest steps that pluripotent stem cells take when they exit this state and start to differentiate. Several previous studies had identified the molecular mechanisms underlying pluripotency maintenance; however, what was lacking when she started her research was an understanding of how pluripotency regulatory control is disrupted as cells exit the pluripotent state. She published her first paper in Stem cell reports in 2018 titled as "KLF4 Nuclear Export Requires ERK Activation and Initiates Exit from Naive Pluripotency" which highlighted the first of the event occurring when differentiation of stem cells begins. Her second article "KLF4 protein stability regulated by interaction with pluripotency transcription factors overrides transcriptional control" published in the August 2019 issue of Genes & Development provides significant new insight into the very first steps taken by stem cells when they exit the pluripotent state in order to become more specialized cells.

Her findings implicate the stability of proteins as a major factor in controlling a pluripotent stem cell's state and in the decision to remain a stem cell or transform into a specialized cell. The protein she studied, KLF4, is one of these transcription factors that gives stem cells their unique

properties. Surprisingly, she found that KLF4 protein was maintained in the cell after she reduced Klf4 gene transcription by 90% by using CRISPR/Cas9 genome editing to delete the parts of the genome that are needed to turn on this gene. This was an unexpected result, but it highlights the importance of studying both transcriptional control and mechanisms that affect protein abundance to understand cell behavior. In searching for the explanation to this surprising finding she discovered that in the pluripotent state KLF4 protein is highly stable and able to function in the cell nucleus for many hours longer than all the other pluripotency transcription factors. Degradation of KLF4 protein releases stem cells from the pluripotent state and allows them to proceed towards more specialized cell types. She also found that interfering with KLF4 degradation can lock cells in the stem cell state and prevent their differentiation. These findings indicated that KLF4 protein destabilization is a critical first step in exit from the pluripotent state.

Her findings also have important implications to our understanding of how many types of cancer develop as KLF4 protein is known to be higher in many cancers. Her findings suggest that in addition to looking at how the Klf4 gene is expressed in these cancers we should also look at how the stability of the protein is regulated which could lead to new therapeutic approaches for the treatment of many cancers.