The EphrinB2/EphB4 axis in regulating hESC pluripotency and differentiation

Grant Award Details

The EphrinB2/EphB4 axis in regulating hESC pluripotency and differentiation

Grant Type: Basic Biology II

Grant Number: RB2-01571

Project Objective: the goal was to investigate the ephrinB2 signaling axis in regulating hESC pluripotency and differentiation. PI has examined the picomolar affinity of the Nipah virus envelope glycoprotein (NiV-G) for its receptor, ephrinB2, and developed tools based on this envelope-receptor interaction for a number of studies carried out in this grant.

Investigator:

Name:	Benhur Lee
Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,371,936

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: The EphrinB2/EphB4 axis in regulating hESC pluripotency and differentiation

Public Abstract: Human embryonic stem cells (hESC) have an inexhaustible ability to divide and renew, and under the appropriate conditions, differentiate and change into any cell type in the body. This balance between pluripotency and self-renewal is a complex and carefully choreographed response of the hESC to local microenvironmental cues. Understanding the molecular regulators of this balance, and the various signals that are integrated by hESC to maintain their pluripotency and self-renewal characteristics are critical for the expansion and differentiation of hESC to specific cell types, which is the ultimate goal of regenerative medicine.

EphrinB2 and ephB4 belong to a large family of cell surface signaling molecules, so called receptor tyrosine kinases (RTKs), that mediate and transduce signaling cascades upon interaction with each other. Cell-cell contacts between ephrinB2 and ephB4 expressing cells provide guidance cues for cell migration and boundary formation in many developmental systems such as the formation of neurons and blood vessels. Importantly, ephrinB2 has been determined to be a molecular marker of “stemness” and is expressed in human embryonic stem cells, neural stem cells and hematopoietic stem cells. Its cognate receptor, EphB4, has also been shown to affect mouse ESC fate. Despite much evidence from model systems that ephrinB2/ephB4 axis may be intimately involved in ESC fate (survival, self-renewal, and pluripotency), this particular axis has not been carefully studied in human ESC.

EphrinB-ephB ligand-receptor interactions are promiscuous, and the lack of highly specific reagents to block cognate ephrinB2-ephB4 interactions has hampered studies into the role of this RTK axis in regulating hESC survival, pluripotency and differentiation. Intriguingly, the envelope protein from an exotic and highly lethal virus called Nipah virus, binds to ephrinB2 with high specificity. Using an arsenal of reagents based on engineered versions of this viral envelope protein, which retains the ephrinB2 binding properties without the virulence of the actual virus, we will interrogate the ephrinB2-ephB4 axis in regulating hESC fate. Extant data from murine ESC suggest that EphB4 activation (signaling) not only favors mesodermal differentiation (a germlayer that gives rise to blood cells, endothelial cells, and muscle cells), but that EphB4 inactivation may result in expansion of primitive hematopoietic (blood) stem cells (HSC) while maintaining their "stemness". Understanding the regulation of this signaling axis could improve the culture of hESCs and the efficiency of HSC lineage differentiation, both key barriers in the field.

Statement of Benefit to California:

Human embryonic stem cells (hESC) have the potential to be a game changer in the practice of medicine. This is due to their apparent inexhaustible ability to divide and renew, and under the appropriate conditions, differentiate and change into any cell type in the body. In theory, scientists could differentiate hESC into any desired cell type in the test tube and use them to replace the desired cell type that is defective or wanting in the patient. This is the promise of regenerative medicine. However, the translation of this technology to actual patient use depends on a better understanding of how pluripotency (the ability to develop into any cell type) is maintained, and the specific conditions under which a particular cell type can be differentiated. This proposal will benefit California by seeking a better understanding of these processes, which will bring us closer to realizing the dream of regenerative medicine, and fulfilling the intent of Proposition 71.

Our proposal seeks to understand how a particular set of cell surface signaling molecules interact, and how these interactions lead to the maintenance of pluripotency or how they may skew hESC towards differentiation to a specific cell lineage. These cell surface signaling molecules are called ephrinB2 and ephB4, and their cognate interactions are known to trigger a cascade of intracellular signals that then determine the fate of hESC. Despite tantalizing evidence from animal model systems that the ephrinB2/ephB4 axis is important for many aspects of ESC fate, it has been difficult to interrogate this axis in human ESC biology due to the lack of highly specific reagents that can block this axis. This proposal capitalizes on a tool that Nature has "unwittingly" provided from an unexpected source. The viral envelope protein from an exotic virus (called Nipah virus) can bind to ephrinB2 with extraordinarily high specificity and block its interaction with ephB4. Using an arsenal of reagents based on this viral envelope protein, we will properly interrogate the role of the ephrinB2/ephB4 axis in hESC fate and development. Understanding the regulation of this signaling axis could improve the culture, expansion, and efficiency of lineage differentiation of hESCs, all key barriers in the field.
