**Single cell heterogeneity underlies pluripotency**

**Abstract**

Embryonic development is a process of creating heterogeneity. In model organisms, non-cell-autonomous mechanisms such as morphogen gradients have been extensively explored. However, our knowledge about cell-autonomous mechanisms controlling cell-to-cell variation is limited. In this talk, I suggest that stem cell populations utilize the intrinsic variation in single cell G1 length to generate different fates during differentiation. Single human embryonic stem cells (hESCs) have different and biased differentiation potentials toward either neuroectoderm or mesendoderm depending on their G1 lengths even before the onset of differentiation. Therefore, single cell variation in G1 length establishes a probability distribution that determines the fate of the population. Furthermore, I suggest molecular and cellular mechanisms to link G1 length to stem cell fates. Primary cilium whose expression is tightly controlled by G1 length translates G1 length information into cellular signaling through autophagy and Nrf2. Increased ciliation during hESC differentiation toward neuroectoderm induces autophagy that results in the inactivation of Nrf2 and thereby relieves transcriptional activation of OCT4 and NANOG. Nrf2 binds directly to upstream regions of these pluripotency genes to promote their expression and repress neuroectoderm derivation. Only after these events had been initiated do neural precursor markers get expressed. Thus we have identified a primary cilium-autophagy-Nrf2 (PAN) control axis coupled to cell cycle progression that determines hESC fates. All together, these findings provide novel mechanisms through which hESCs create heterogeneity during differentiation.