Department of Chemistry and Molecular Biology
and NIH Center for Protease Research
Seminar
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3:45 pm in Dunbar 152

"*Transcription Factors that Orchestrate the Self-Renewal and Pluripotency of Embryonic Stem Cells Function as Molecular Rheostats***"**

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Abstract

The transcription factor Sox2 functions as a master regulator during mammalian development and during the reprogramming of somatic cells to a pluripotent stem cell state. To understand the roles of Sox2 more fully, we have been examining how the levels of Sox2 regulate the fate of embryonic stem (ES) cells. Previously, we determined that transient elevation of Sox2 levels in ES cells decreases the expression of at least five genes that are essential for maintaining the properties of ES cells (Boer et al, *Nucleic Acids Res* 35:1773-86, 2007). This finding led us to test the hypothesis that increasing the levels of Sox2 in ES cells would trigger their differentiation. After engineering Sox2-inducible ES cells, we determined that small increases in Sox2 levels (<2-fold) rapidly induce their differentiation (Kopp et al, *Stem Cells* 26:903-11, 2008). *These and other studies demonstrate that Sox2 functions as a molecular rheostat to control the fate of ES cells.* To begin to determine how small increases in Sox2 trigger the differentiation of ES cells, we recently performed an unbiased proteomic screen of Sox2-interacting proteins using mass spectrometry. This analysis identified >40 nuclear proteins in ES cells that associate with Sox2. We verified the interaction of Sox2 with several of these proteins, including another Sox family member, Sox21. Currently, we are extending these bindings by investigating the expression and function of Sox21, because Sox21 is one of the first genes to be induced during Sox2-mediated ES cell differentiation, and because Sox21, unlike Sox2, appears to be a pure transcriptional repressor. Our studies indicate that the regulation of the Sox21 gene provides an excellent model for understanding the mechanisms by which "bivalent genes" are activated rapidly during development. (Bivalent genes contain both activating and silencing histone modifications.) Finally, we tested the hypothesis that expression of Sox21 in ES cells is sufficient to trigger their differentiation. After engineering Sox21-inducible ES cells, we determined that premature expression of Sox21 induces ES cells to differentiate. Together, our studies led to the conclusion that Sox proteins, in particular Sox2 and Sox21, must be precisely regulated, both quantitatively and qualitatively, during mammalian development.