OMICS Group Conferences
Accelerating Scientific Discovery
3rd World Congress on
Cell Science & Stem Cell Research
November 20- 22, 2013 DoubleTree by Hilton Baltimore-BWI Airport, USA

Id2 expression determines cell fate in multipotent progenitor cells

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Abstract

The survival, self-renewal and differentiation of hematopoietic stem and progenitor cells (HSPCs) and their progeny is maintained by tightly controlled expression of transcription factors and their regulators. Deregulations of these control programs are responsible for disease states including leukemia, lymphoma, and/or anemia. Id2 is a member of the helix-loop-helix (HLH) family of transcription factor regulators, and is essential for the development of several hematopoietic lineages, including natural killer (NK) cells and dendritic cells. However, less is known about the expression and function of Id2 in early stages of hematopoiesis. Therefore, we generated an Id2-EYFP reporter mouse model, inserting the cDNA encoding enhanced yellow fluorescent protein (EYFP) into the Id2 locus. This allowed us to examine the expression of Id2 during the development of all lineages throughout hematopoiesis. As predicted, Id2 is expressed in mature hematopoietic lineages, including NK and dendritic cells. In addition, it is also expressed in mature neutrophils and monocytes. Id2 expression is suppressed during B cell and erythroid development, and it is dynamically regulated during T cell development. Moreover, we discovered that the levels of Id2 are directly correlated with cell fate in HSPCs. First, common myeloid progenitors (CMPs) with high levels of Id2 expression are precursors for granulocyte/macrophage progenitors (GMPs), while CMPs with low Id2 are precursors for megakaryocyte/erythrocyte progenitors (MEPs). Second, we found that multipotent progenitors (MPPs) with high Id2 expression (EYFP-high cells) showed increased myeloid and decreased lymphoid development in vivo, compared with EYFP-low cells. We also determined that Id2 is highly expressed in hematopoietic stem cells (HSCs). Additional data suggest that Id2 is required for the self-renewal function of HSCs during serial transplantation. These data elucidate the role of Id2 in self-renewal and cell fate determination in HSPCs, and contribute to a better understanding of the transcriptional regulatory networks necessary for functional hematopoiesis.

Biography

Dr. Lei Sun obtained his Ph.D. in Stem Cell Biology and Developmental Biology under the direction of Dr. Ying Jin from Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, where he characterized Stk40 as a differentiation determinant in mouse embryonic stem cells. He did postdoctoral work on the molecular mechanisms governing the biology of prostate and pancreatic cancer stem cells in Dr. William Farrar's lab at the National Cancer Institute-Frederick. He then joined Dr. Jonathan Keller's lab where he has continued a longstanding interest in the molecular and cellular regulation of hematopoietic stem cell growth and differentiation.