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Autophagy in hematopoiesis and leukemogenesis

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Autophagy, unique protective cytoplasmic machinery involving lysosomal degradation, is required for hematopoietic stem cell multilineage differentiation that protects against leukemogenesis, but the underlying mechanism is unknown. We uncovered a mechanistic link between autophagy and hematopoietic stem cell differentiation. Physiological autophagy activity was found to be inversely correlated with Notch signaling during hematopoietic stem cell differentiation whilst pathologically low autophagy activity was associated with upregulated Notch signaling in dysfunctional hematopoietic stem cells of leukemia patients. Furthermore, we show that autophagy directly degrades intracellular Notch whereas conditional autophagy defects lead to elevated intracellular Notch and its downstream targets as well as failed hematopoietic stem cell differentiation. Hematopoietic stem cell differentiation potential, however, was restored in an autophagy defective system when Notch signaling was pharmacologically or genetically abrogated. Finally, we identified mitochondrial reactive oxygen species (ROS) as an upstream trigger for autophagy to physiologically downregulate Notch signaling and drive hematopoietic stem cell differentiation. Hence, in the cause of development when mitochondrial ROS are progressively produced, autophagy is triggered by the ROS to target Notch signaling to sustain hematopoietic stem cell differentiation. Autophagy dysfunction is attributed to the differentiation blockades which are often the cause of hematological malignancies. Therefore, our present findings provide a critical insight into the current mechanistic understanding of physiological and pathological connections between autophagy and hematopoietic stem cell differentiation, thereby proposing a novel mechanism by which autophagy maintains hematopoiesis and protects against leukemogenesis.

Biography

Jianrong Wang earned his PhD degree in The Shanghai Institute of Biochemistry, Chinese Academy of Sciences in July of 1997. In October of that year, he was appointed as a Research Professor in a municipal institute in Shanghai China. After moving to US in January of 1999, he conducted research primarily at Cornell University. In March of 2010, he was offered a professorial position at the Hematology Center of Cyrus Tang Medical Institute Soochow University. His laboratory focuses on the understanding of the biology of autophagy in hematopoiesis and leukemogenesis, with an ultimate goal of preventing hematological oncogenic germination by protecting normal stem cells from malignant transformation.

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