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Potential of small molecule inducers in cell-based therapeutics

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Many diseases and conditions, including cancer, AIDS, aging, congestive heart failure and chronic obstructive pulmonary diseases can cause debilitating muscle wasting disorders. Stem cell-base therapies have emerged as potential therapeutics for muscle wasting disorders. However, many challenges remain and deciphering the molecular mechanisms of myogenic differentiation will be a critical step in developing the best strategies to enhance stem cell-mediated muscle regeneration. We have found that retinoic acid (RA), an agonist of retinoic acid receptor (RAR), enhances myogenic conversion through the histone acetyltransferase (HAT) p300 and histone acetylation at myogenic related loci. We have also found that an agonist of retinoid X receptor (RXR) is a more efficient enhancer than RA for myogenic conversion of ES cells in a RAR-independent manner, suggesting a novel transcriptional program is involved. Recently, we have examined the temporal events of HAT association and histone acetylation at different myogenic loci. Our data revealed that the HAT p300 is stepwise enriched at distinct myogenic regulatory regions during myoblast differentiation and correlates positively with histone acetylation. Inhibition of p300 HAT activity results in the decrease in histone acetylation and myoblast differentiation. Moreover, different transcription factors appear to play distinct roles in the stepwise recruitment of p300 to the myogenic loci. We show for the first time that p300 is directly involved in the early regulation of myogenic enhancer, and provide molecular insights into how the p300 HAT activity, histone acetylation and transcription factor occupancy are related to enhancer activation and gene transcription. Our studies shed new light on how different signaling pathways and chromatin dynamics converge to direct stem cell differentiation.

Biography

Qiao Li received her MD and MSc degrees from the Norman Bethune University of Medical Sciences of China. She completed her study at the Karolinska Institute of Sweden, and continued her research on chromatin and gene regulation at the National Institutes of Health of USA. Thereafter, she established her independent research program at the University of Ottawa. She has devoted her research efforts to the regulatory mechanisms of gene expression. She has made important contributions to the understanding of how chromatin dynamics and various signaling pathways crosstalk and how cells respond to regulatory signals in the context of chromatin. Recently, her research team has focused on how chromatin dynamics and different signaling pathways converge to direct stem cell differentiation.

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