Conférence du Centre de recherche de L'Hôtel-Dieu de Québec

Le Centre de recherche en cancérologie de l'Université Laval

Conférencière

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Invitée par Dr Jacques Côté

Titre: New Functions for Gcn5 and SAGA

We have a long-standing interest in understanding how chromatin organization regulates nuclear processes. Our research is directed at defining the functions of histone modifying enzymes both in normal biological processes and in disease states, using genetic approaches in yeast, in mice, and in human cells. Our recent experiments have revealed new and unexpected functions for several histone modifying enzymes and have demonstrated that these enzymes are important not only to the regulation of gene transcription but also to diverse processes including mitosis, protein stability, and telomere maintenance.

To understand the functions of the Gcn5 acetyltransferase, we have created a series of mutations in the mouse *Gcn5* gene. Deletion of *Gcn5* leads early embryonic death and to telomere dysfunction. Biochemical studies reveal that depletion of Gcn5 or ubiquitin specific protease 22 (Usp22), which is another bona fide component of the Gcn5-containing SAGA-type complex, increases the turnover of two shelterin proteins, TRF1 and POT1a. Inhibition of the proteasomes opposes this effect. The Usp22 deubiquitylating module requires association with SAGA complexes for activity, and we find that depletion of Gcn5 compromises this association in mammalian cells. Overall, these results indicate that Gcn5 regulates TRF1 levels through effects on Usp22 activity and SAGA integrity. These studies provide the first indication that Gcn5 and mammalian SAGA influence telomere maintenance and the first demonstration that SAGA affects protein stability. Current studies are directed at identifying additional USP22 targets.

We have also created *Gcn5* null ES cells. Upon removal of LIF, these cells lose pluripotency more quickly than do wild type ES cells. Preliminary data suggest that Gcn5 may be a key regulator of the master transcription factors required for maintenance of the pluripotent state.

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