EDITORIAL

The Ribosome is No Longer Just the Housekeeper: Ribosome Synthesis and Function as a Target for Therapy

Ribosome biogenesis has long been seen as a housekeeping process with ribosomes seen as highly stable 'constants' within a cell and rRNA the most used loading control in microarray mRNA expression experiments. However, the pioneering studies of Venkatraman Ramakrishnan, Thomas Steitz and Ada Yonath defining the structure of the ribosome heralded a new era in understanding the importance of ribosome function and culminated in them sharing the Nobel Prize in Chemistry in 2009. It is now clear that precise regulation of the synthesis and function of ribsomes is not only essential for protein translation and cell growth, but is also critical for cellular control of apoptosis, senescence, DNA damage and even aging.

Unexpectedly, ribosomal RNA genes are early response genes and levels of ribosome synthesis are acutely and exquisitely regulated through the normal cell cycle. Furthermore, the efficiency of translation of specific mRNAs alters with relative amount of ribosomes as well as with post-translational modification of the ribosomes themselves and of myriad associated translation factors. An additional level of translational control is imposed by factors, including microRNAs that target individual mRNAs for degradation and/or translational down-regulation.

Overlaid with the critical role of ribosome biogenesis in the regulation of protein synthesis and the changing patterns of protein expression with altered extracellular signals, evidence is now emerging that individual ribosomal proteins within the nucleolus, generated by the failure of ribosome biogenesis, are actively involved in sensing and responding to nucleolar/cellular stress, activating the p53 pathway and inhibiting growth and proliferation.

Consistent with the critical nature of tightly regulated protein synthesis in normal cell function, disruption of this process is observed in a range of diseases characterised by tissue overgrowth. Importantly, dysregulation of ribosome function ('ribosomopathy'[1]) is emerging as a critical driver of disease. Understanding the intricate mechanisms underlying its control is now providing novel therapeutic targets and opportunities.

The four articles highlighted here provide complementary descriptions of the key observations that have begun to reveal the importance of exquisite regulation of ribosome function at multiple levels, definition of the key players in executing this regulation, their complex interactions and their potential for exploitation in the treatment of disease. Kate Hannan and Rick Pearson review the signal transduction pathways downstream of PI3K that coordinate ribosome synthesis and function. They further describe how members of this pathway interact with signalling from the two other major growth control oncogenes, MYC and RAS, and the implications this has in cancer. Jane Lin, Nicola Crana and Leonie Quinn elucidate the central role of MYC in modulating ribosome biogenesis and cell growth, drawing on data from both mammalian and *Drosophila* systems. Jennifer Clancy and Thomas Preiss complement these reviews by presenting the latest data defining microRNAs as a major new class of regulators of ribosome function that modulate the stability of specific mRNAs and their efficiency of translation and are implicated in cardiac disease. Finally, Elaine Sanij, Nadine Hein and Ross Hannan describe how the levels of ribosome biogenesis and hence nucleolar conformation are intimately involved in the monitoring of cellular stress and play a central role in controlling cell cycle arrest, senescence and apoptosis.

Consigned for so long as part of a passive housekeeping process, the control of ribosome synthesis and function is now taking centre stage as a key regulatory point in disease. It appears the housekeeper is keeping the house.

1. Luft, F. (2010) *J. Mol. Med.* **88**, 1-3

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Cover Illustration

Localisation of upstream binding factor (UBF; red) and ribosomal DNA (rDNA; green) in the nucleolar organiser regions.
Image courtesy of Ross Hannan, Peter MacCallum Cancer Centre.

The Ribosome in Health and Disease

Guest Editor: Richard Pearson

In the next issue...
In April, the Showcase on Research will be on **Molecular Aspects of Reproduction** – *Guest Editor: Peter Koopman*