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Cancer Genomics: the post-transcriptional era

Editorial overview

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Nahum Sonenberg is a James McGill Professor in the Department of Biochemistry and the Goodman Cancer Research Centre at McGill University. He discovered the mRNA 5' cap-binding protein, eIF4E, and the eIF4E-binding proteins (4E-BPs). He demonstrated that the 4E-BPs are phosphorylated downstream of the PI3K/Akt/mTOR pathway. He also showed that eIF4E is a proto-oncogene. He developed cell-free systems to study the mechanisms by which miRNAs inhibit gene expression.

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Nissim Hay is a professor in the Department of Biochemistry and Molecular Genetics at the University of Illinois, Chicago. He is interested in the roles of Akt and mTOR in the genesis of cancer. His laboratory showed that Akt is sufficient and required for the activation of mTORC1 by growth factors, and that mTORC1 and mRNA translation are critical effectors of Akt mediated tumorigenesis.

There have been major efforts in the past decade to decipher the secrets of cancer through genomic sequencing and gene expression profiling, with the ultimate goal of providing 'personal treatment'. However, there is now strong evidence documenting a critical role of post-transcriptional mechanisms through mRNA translation and non-coding sequences in the etiology of cancer. In this issue of Current Opinion in Genetics and Development, there are eight articles describing mechanisms of post-transcriptional regulation and mRNA translation that impact or could potentially impact cancer development.

The role of microRNAs in the genesis of cancer that was barely mentioned only a decade ago is now well documented. MicroRNAs are single stranded RNA of 19–21 nucleotides, which suppress gene expression by binding to mRNAs primarily at the 3′UTR to inhibit translation and/or their promote degradation. During the last decade ample evidence has accumulated that microRNAs are deleted or overexpressed in cancer cells and contribute to the cancer phenotype. The first article by Carlo Croce and Gianpiero Di Leva provides up to date information on using microRNAs profiling in biological fluids as non-invasive methods for early detection of cancer and for prognosis.

Matheetrairut and Slack describe a new aspect of the miRNA–cancer connection, which involves the interplay between cellular responses to ionizing radiation (IR), double-stranded breaks (DSB), and miRNAs. The review covers many of the most significant miRNA:mRNA target pairs involved in cellular responses to IR. The emphasis is on let-7, miR-34, and miR-21 and their embedding within their key cascades, such as p53 and ATM.

Recently, there has been a dramatic increase in the understanding of the mechanisms by which mRNA binding proteins control mRNA processing, stability, and translation. RNA–protein complexes also modulate the activities of microRNAs. The article by Thomas Tuschl and colleagues emphasizes the increased versatility of posttranscriptional mechanisms that regulate gene expression. The article is focused on RNA–protein interactions and describes methods to define these interactions and their regulatory networks.

Paul Fox and colleagues review recent discoveries about mRNA translational control through the 3′UTR, and regulation by environmental inputs. The article describes protein complexes that bind to the *cis*-acting structural RNA elements in the 3′UTR and how they interact with microRNAs to regulate mRNA translation. Jack Keene and Laura Simone describe how a

subset of RNA binding proteins termed ELAV/HU bind AU-rich RNA binding sites and antagonize the destabilization effect of microRNA.

Gregory Hannon *et al.* describe the role of another prominent class of small RNAs, piRNAs, which play a critical role in maintaining the integrity of the genome of germ call from the harmful effects of transposon elements. This could be of a potential relevance to cancer where disruption of genome integrity is a hallmark of carcinogenesis.

The mammalian target of rapamycin complex 1 (mTORC1), comprising mTOR and other accessory proteins that determine its activity, is a regulator of mRNA translation whose activity is mediated by nutrients and growth factors. It promotes the synthesis of a subset of proteins through the phosphorylation and inactivation of the repressors of mRNA translation eIF4E binding proteins (4E-BPs), and through the phosphorylation of S6 kinase. Another structurally and functionally distinct complex of mTOR, mTORC2, is an upstream regulator of Akt and other AGC kinases. Both mTORC1 and mTORC2 are frequently activated in human cancers. Rapamycin analogs, which inhibit mTORC1, are used in the clinic, while new inhibitors of mTORC1 and mTORC2 are in clinical trials. The article by Michael Hall and colleagues describes signaling pathways mediated by mTOR complexes that control multiple metabolic pathways within the cell at both the mRNA translation level and posttranslational level through protein phosphorylation.

Finally, Thomas and colleagues bring into focus the emerging role of defects in ribosomes, and in particular ribosomal proteins engender cancer. They summarize the current literature regarding the molecular basis for a large group of inherited diseases associated with mutations in ribosome components, referred to as ribosomopathies. These inherited diseases share common pathological features including significant developmental defects, hematological abnormalities, and high cancer susceptibility.