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Editorial overview: Cancer genomics: RNA metabolism and translation in cancer pathogenesis and therapy

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Major advances in our understanding and therapy of cancer have come from large-scale coordinated efforts to obtain complete catalogs of the genomic alterations in cancer. These efforts have uncovered novel oncogenic pathways, motivated development of new therapeutic approaches, identified biomarkers for immunotherapy, and highlighted the importance of epigenetic alterations. While the cancer genome has been heavily interrogated by these efforts, our understanding of how post-transcriptional regulation promotes tumorigenesis is still in development. This issue of *Current Opinion in Genetics & Development* presents a series of articles related to aberrations in RNA metabolism and mRNA translation in cancer, and novel therapeutic approaches targeting diverse aspects of the RNA lifecycle.

There are numerous opportunities along the process of generating RNA and protein that may promote cancer development. First, a single gene may give rise to many gene products through alternative splicing as well alternative 3' end formation or promoter usage. Altering the messenger RNA (mRNA) products of a single gene may impact their coding capacity, stability, translation, and/or localization, and ultimately, the function and expression of the final protein product. As reviewed by Siegfried and Karni, there are numerous examples where altered splicing of pre-mRNAs encoding targets of anti-cancer therapies has resulted in novel mechanisms of drug resistance. Moreover, recent cancer genome sequencing studies have uncovered frequent mutations in genes encoding RNA splicing components themselves in a variety of cancer types. As described by Clara Kielkopf, intersecting these genomic data with recent insights into the structure of spliceosomal proteins has revealed potential mechanisms by which splicing factor mutations dysregulate the process of RNA splicing.

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In addition to pre-mRNA splicing, there are numerous ways in which the cellular mechanisms regulating the quantity and quality of RNA may be perturbed in cancer. Key amongst these is nonsense-mediated decay (NMD), a process whereby mRNAs are inspected for premature termination codons primarily introduced through DNA mutations or RNA splicing defects. As reviewed by Popp and Maquat, mutations leading to NMD are relatively frequent in tumor suppressors, and modulation of NMD is used by cancerous cells to support survival under stress. Less understood are epitranscriptomic events, including alterations of the nucleotides of RNA through modifications as well as editing. For example, a role for *N*⁶-methyladenosine (m⁶A), the most abundant internal modification in eukaryotic mRNAs and noncoding RNAs (ncRNAs), and its writers, readers, and erasers has been proposed in a variety of cancer types, as reviewed by Deng *et al.* m⁶A modification has been shown to impact nearly every step of RNA metabolism depending on the location and extent of the modification on RNA, attesting to its potential in cancer. Similarly, there are diverse functional consequences of editing nucleotides within RNAs. As reviewed by Xu *et al.*, RNA editing is a post-transcriptional process whereby individual nucleotides in RNA are exchanged to alter the final RNA coding sequence. The most common form of RNA editing is adenosine-to-inosine ('A-to-I') editing and recent analysis of the A-to-I RNA-editing landscape has identified increased editing in tumors relative to normal tissues in most cancer types. The vast majority of A-to-I editing occurs in 3' untranslated regions (UTRs), introns, and intergenic regions but some occurs in coding regions with diverse consequences.

Novel genomic approaches characterizing the cancer transcriptome have resulted in important advances described in many articles of this issue. For example, as noted by Patop and Kadener, characterization of the expression of exonic circular RNAs (circRNAs) has been made possible through RNA sequencing that does not rely on poly(A) purification combined with the development of specific algorithms. While high cellular division rates appear to be inversely correlated with circRNA production, many interesting examples of cancer-specific roles of circRNAs are emerging. There are even examples of circRNAs produced from well-described oncogenic chromosomal rearrangements in cancer such as MLL-AF9, PML-RARA, and EWSR1-FL1 fusions. Related to the generation of chimeric RNAs, Li *et al.* describe non-canonical mechanisms by which chimeric RNA species may be produced in cancer cells by means beyond chromosomal rearrangements, including *trans* splicing and *cis* splicing between adjacent genes.

As noted above, a variety of ncRNA species play important roles in cancer pathogenesis. Two articles in this issue center on micro-RNAs (miRNAs) and long noncoding RNAs (lncRNAs). lncRNAs are defined as RNA transcripts of >200 nucleotides without apparent protein-coding potential. As described by Hu *et al.*, only a small proportion of the lncRNAs in the human genome have been explored to date but many appear to be cancer-specific or altered in cancer relative to normal tissues in specific ways. In contrast to lncRNAs, miRNAs have been long known to affect cancer progression. miRNAs are small (19–24 nucleotide) RNAs that modulate the stability and translation of specific mRNAs by virtue of their binding to complementary sites, usually located in the 3' UTR of the transcript. While miRNAs have most heavily been studied in their ability to modulate gene expression, recent data described in the review by Vannini *et al.* show that miRNAs may also be secreted by

cells and bind specific protein receptors (so-called ‘miRceptors’), serving as mediators of inter-cellular communication.

Much of the regulation of RNA metabolism occurs by diverse families of RNA binding proteins (RBPs) that mediate virtually every stage of the RNA life cycle. Recent systematic analysis through RNA interactome capture described by Moore *et al.* have identified a host of new RBPs. Notably, hundreds of them are potentially linked to cancer progression, and many are unorthodox in the sense that they carry non-canonical RNA binding domains. Cancer-associated mutations and mis-expression of RBPs impact nearly all stages of RNA metabolism including RNA splicing, 3' end processing, editing, stability, storage, localization, translation, and RNA biogenesis (including generation of miRNAs). Interestingly, as reviewed by Bisogno and Keene, many RBPs and ncRNAs appear to work together in coordinated units, so-called ‘RNA regulons’, to regulate the expression of functionally related RNA species. Thus, RBPs emerge as key regulatory nodes of functionally inter-connected RNA networks that preserve cell homeostasis and whose alteration contributes to cancer development.

While altered RNA processing clearly has an important influence on protein production, much regulation occurs at the level of mRNA translation, as described in a series of articles in this issue. Alterations in mRNA translation are well established in cancer, as mitogenic signaling through the RAS/PI3K/AKT/mTORC1 pathway stimulates formation of the eIF4F complex and translation initiation, while oncogenic stimulation by MYC promotes the biogenesis of many components of the translation machinery. This generates a ‘surplus’ of translational activity to which cancer cells become addicted and that can be targeted for therapy. A general overview of translation initiation factors and their relevance in cancer is provided by De la Parra *et al.* In addition, cancer-associated alterations in ribosome biogenesis are described by Bustelo and Dosil. Translation is highly interconnected with metabolism and autophagy, and this cross-talk is the subject of reviews by Lindqvist *et al.*, and Biffo *et al.* Translational reprogramming is at the base of cancer progression, and Harvey and Willis describe how tumors hijack major stress response pathways (the unfolded protein response and DNA damage response) to reprogram translation and promote cell survival and therapeutic resistance.

Much of the information described above provide new concepts for cancer pathogenesis based on alterations in RNA processing and translation. At the same time, this information is providing a wide variety of new therapeutic approaches for cancer. For example, Chu *et al.* review a variety of therapeutic nodes targeting eIF4F in cancer. In addition, the discovery of cancer-associated RNA splicing factors has identified the unique dependence of cells bearing these mutations on otherwise normal splicing catalysis. This finding has resulted in a variety of pharmacologic approaches to target splicing in cancer reviewed by Agrawal *et al.* Beyond these specific reviews, nearly every article in this issue describes some novel therapeutic implication of altered RNA processing and translation in cancer. Indeed, targeting novel cancer cell dependencies on RNA modifications, lncRNAs, splicing, and NMD are all exciting therapeutic avenues being explored in addition to continued efforts to target miR-NAs and mRNA translation.