The dysregulation of protein synthesis is an emerging hallmark of cancer, with altered translation being essential for the induction of oncogenic gene programmes. Tumour cells require enhanced production of proteins that drive cellular growth and division, while the stromal compartment is mainly engaged in producing extracellular proteins needed to create the microenvironment essential to support the growth of the tumour. These distinct programmes of gene expression drive tumour growth and create the supportive environment in which it flourishes. Our research is directed at understanding how certain core components of the translation machinery can selectively increase the rate of translation of key mRNAs encoding oncogenic proteins.

Understanding mechanistically how eIF4A1 drives tumorigenesis RNA helicases are critical in sculpting and unwinding RNA structures, which are composed of a loading subunit and one or more unwinding subunits. Moreover, the rate of unwinding is essential to support the growth of the tumour. These distinct programmes of gene expression drive tumour growth and create the supportive environment in which it flourishes. Our research is directed at understanding how certain core components of the translation machinery can selectively increase the rate of translation of key mRNAs encoding oncogenic proteins.

Understanding mechanistically how eIF4A1 drives tumorigenesis RNA helicases are critical in sculpting and rearranging mRNA secondary structure within cells. As such, these enzymes play pivotal roles in every stage of the mRNA lifecycle. One such critical RNA helicase is eIF4A1, which is responsible for the rate-limiting initial step of mRNA translation. While all mRNAs require eIF4A1 for their translation, it is now clear that oncogenic mRNAs are more dependent on this process for their translation, through the unwinding of RNA structures within their 5′UTR. Importantly, eIF4A1 activity is frequently increased in tumour cells and as such a number of companies are developing drugs which target it for the treatment of cancers. Our recent work has uncovered unforeseen mechanistic insights on how this helicase functions to specifically promote oncogenic gene expression. We find that efficient unwinding of RNA secondary structure requires eIF4A1 to act in a multimeric form, composed of a loading subunit and one or more unwinding subunits (Fig 1a), which we have shown occurs both in vitro (Fig 1b) and in cells (Fig 1c). Moreover, the rate of unwinding is dependent on the sequence of the single stranded region of RNA bound by the loading subunit of eIF4A1, and highest levels of unwinding occur when this region is composed entirely of purines (Fig 1d). Our RNA structure probing data shows increased secondary structure roughly 30–50nt downstream of 10nt stretches of purines in cells following eIF4A1 inhibition (Fig 1e) and in vitro translation assays show that adding a purine-rich sequence 30nt upstream of a hairpin was able to alleviate the inhibitory effect on translation (Fig 1f). Our data suggest that oncogenic mRNA translation is being driven by eIF4A1 through its role in unwinding RNA structure as a multimeric complex during scanning and that this is distinct from its role during ribosome recruitment.

Oncogenic gene programmes, codon usage and modulated mRNA translation

The degeneracy of the genetic triplet code means that multiple codons encode the same amino acid. It was long believed that in complex organisms the redundancy within the code had no functional consequences. However, the passive nature of decoding has been challenged and it is now clear that synonymous codon usage affects the expression of proteins through altering the rate of translation elongation and the mRNA half-life. Critically, the expression of synonymous mRNAs is profoundly different in proliferating cells compared to differentiated cells and in tumours compared to normal tissues (Grigoldi et al. Cell 2014). Moreover, the anticodon signature of mRNAs in cancer cells specifically matches the codon composition of mRNAs required for cell proliferation. These observations suggest that genes required for proliferation are stabilised at the mRNA level and highly expressed in neoplastic diseases due to the embedded codon usage and the levels of corresponding mRNAs. Using a combination of mRNA-seq and RNA-seq we show that in human fibroblasts, mRNAs with A/U ending codons are more highly expressed in proliferative conditions (fed) compared to when serum starved (Fig 2A).

Indeed the RNA profile matches this, with RNAs containing A or U at the wobble position of the anticodon being more highly expressed in fed vs starved cells (Fig 2B). Recent data from yeast has shown that the CCR4–NOT component NOT5 is essential to support the growth of the tumour. These distinct programmes of gene expression drive tumour growth and create the supportive environment in which it flourishes. Our research is directed at understanding how certain core components of the translation machinery can selectively increase the rate of translation of key mRNAs encoding oncogenic proteins.

What remains unknown is how the stoichiometry of the RNA pool, and the proportion of RNAs charged with amino acids, relates to the synonym usage changes in different cellular states and tumour tissues. We are currently conducting RNA sequencing in proliferative and quiescent cells as well as different tumour models in the institute to address these questions. These approaches will then be used to determine how these processes define and dictate the different gene expression programmes within the tumour environment and whether either specific RNAs or amino acids could be possible candidates as therapeutic vulnerabilities.

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