Ribosomal RNA epitranscriptomic alterations in cancer and their contribution to specific mRNA translation

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Background: Long regarded as a passive player in protein synthesis, the ribosome is now recognized as an active regulator of mRNA translation. This function is driven, in part, by the heterogeneity of ribosome composition, including chemical modifications of ribosomal RNA (rRNA). We and others have recently shown that rRNA 2'-O-methylation (2'-O-Me), a modification guided by small nucleolar RNAs (snoRNAs), is profoundly altered across multiple cancer types including breast cancer, lymphoma, leukemia and high-grade gliomas. Altered 2'Ome patterns have been associated with clinical features and cellular phenotype such as stemness and may serve as biomarker. However, the molecular mechanisms by which these modifications regulate ribosome activity and mRNA translation remain largely unknown. Method: By exploiting both physiological and pathological variations of 2'Ome together with ribosome structure–function relationships, we aimed to identify specific methylation sites that regulate ribosome activity and translational control. To this end, we have developed tools and models for sitespecific manipulation of 2'Ome through their corresponding guide snoRNAs to generate robust models to investigate their functions. Results: We have identified several regulatory 2'Ome sites, including 18S-Gm1447 guided by SNORD127, regulating normal and stress-induced translation, in particular that of IRES-containing mRNAs. Importantly alteration of single 2'Ome site was sufficient to modulate translation, supporting the view that the role of epitranscriptomic marks should be considered both individually and cooperatively. Conclusion: Our findings support the emerging concept of ribosomal epitranscriptomic regulation of translation and establish ribosome remodeling as a key feature of cancer cells that contributes to the control of tumor cell phenotypes.