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Commentary

The epitranscriptome: At the crossroad of cancer prognosis

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Recent findings have identified methylation occurring at the cytosine of mRNA as a new epitranscriptomic mark beyond the methylation of the adenine [1]. These marks open new biological horizons and define the existence of other possible mechanisms that do not correlate with alteration of the genetic sequence, epigenetic modifications or even post-translational modifications. The epitranscriptome identifies methylation occurring at the transcript level, which were once invisible [2], and that could be responsible for the maturation and translational processing of mRNAs. Once more, epi-marks claim their role in cellular processes and further confirm their involvement as key players in cell fate decisions.

Epitranscriptomic modifications have been identified in cancer cells. In particular, methylation at the N6 adenosine of METTLR3 and IKHB5 mRNAs occur in bladder cancer, inhibit ITGA6 expression, and correlate with poor prognosis [3]. Recent advances have highlighted epitranscriptomic processes in pancreatic cancer too. In a study recently published in *EBioMedicine*, methylation occurring in total cellular mRNA at cytosine 5 decreased in patients affected by pancreatic cancer. The methylation status correlated with clinicopathological parameters such as T stage, proliferation index, tumour recurrence and survival. Furthermore, the authors identified that m5C level correlated with decreased expression of the methyltransferase NOP2/Sun RNA Methyltransferase 6 (NSUN6) [4]. The importance of its activity was recently determined by observing augmented translation of those mRNAs, that were methylated by NSUN6 [5, 6]. The emerging role of NSUN6, and m5C methylation mediated by its activity, has been also found in gastrointestinal and head and neck cancers [7, 8]. The study of Yang and colleagues showed for the first time the involvement of NSUN6 and its relation to m5C methylation in pancreatic cancer. The peculiar mechanism of translational processing stands at the crossroads between epigenetic modification (occurring at the genome level), and the interaction between mRNAs and their counterparts with inhibitory function (small-non-coding RNAs). Interestingly, methylation occurring at the adenine and the cytosine of mRNA act differently than in the corresponding DNA. Epigenetic methylation of DNA is responsible for silencing the genetic sequence, to stop transcription. Instead, methylation occurring on mRNA bases promotes nucleic acid translation.

Methylation could offer new insights in terms of interaction between mRNAs, the RNA-induced silencing complex (RISC), and miRNAs, highlighting new regulatory processes of RNA maturation and the translation machinery. This epitranscriptomic mark might not only affect mRNAs and tRNAs, but also small-non-coding RNA and the long-non-coding RNAs, by modulating affinity for their targets, thus amplifying the role exerted by the methylation of RNA. Of note, putative RNA-only methyltransferases have not yet been identified. It has been shown that DNA methyltransferases (DNMTs) and NSUNs are responsible for RNA methylation, but that they are capable of also methylating DNA [4]. Up to now, their dual function of inhibiting transcription and promoting translation is not clearly understood. Further studies are needed to clarify which regulatory processes modulate the functioning of those methyltransferases at the nuclear and cytosolic level.

In the future, the epitranscriptome could be fully integrated in diagnostic tools for the identification of clinicopathological parameters and offer potential therapeutic insight for the treatment of different tumour types.

Declaration of Competing Interest

The author reports no conflicts of interest.

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