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The mechanism of nonsense-mediated mRNA decay and its players

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Abstract: One third of the gene mutations found in human genetic disorders, including cancer, result in nonsense codons leading to the rapid degradation of their mRNAs by the surveillance mechanism of nonsense-mediated mRNA decay (NMD). However, NMD also regulates the cellular abundance of normal and fully functional mRNAs, targeting about 10% of the mammalian transcriptome. Consequently, NMD plays a critical role in several biological processes by shaping the respective gene expression program. For example, NMD plays roles in the cellular homeostasis, embryonic development, and cellular response to stress. Hence, the NMD response must be under a strict control in order to avoid undesirable alterations to the gene expression program of cells and tissues. Indeed, disturbance of this control mechanism can lead to embryonic lethality and pathologies, including cancer.
NMD is a complex process that relies on numerous players, which interact in a highly organized manner. In vertebrates, at least 10 proteins (UPF1, UPF2, UPF3A, UPF3B, SMG1, and SMG5-9) were shown to be involved in NMD. More recently, some additional proteins were also implicated, but the interactions among these components is only partly known. In addition, some NMD mechanistic aspects suggest that missing roles can be played by proteins still not reported to be involved in this pathway. To tackle this hypothesis, we used a bioinformatic pipeline to predict new NMD players, and we generated a list of NMD candidates. We are currently testing the effect of depleting the most significant candidates on the levels of reporter NMD-targets. At least for two of them, we observe a significant increase in the abundance of canonical NMD substrates, suggesting a function of these proteins in NMD. In this project, we propose to validate these candidates as novel NMD-factors.