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Role of the SMN complex and the methylosome in selenoprotein mRNP assembly and translation

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Selenoprotein synthesis requires the co-translational recoding of an UGA_{Sec} codon. In mammals, this process involves an RNA structural element, called Selenocysteine Insertion Sequence (SECIS) located in the 3'UTR of selenoprotein mRNAs. Essential in this process is the SECIS binding protein 2 (SBP2) that binds the SECIS RNA and recruits translation and assembly factors to the mRNP. SBP2 shares a common RNA binding domain with core proteins of small non-coding RNPs and selenoprotein mRNP assembly is similar to that of snRNPs (splicing) or snoRNPs (ribosome biosynthesis). Our team showed that several selenoprotein mRNAs undergo unusual cap modification and have an hypermethylated m₃^{2,2,7}G cap instead of a classical 7-methylguanosine (m⁷G) (Wurth *et al.*, 2014). m₃^{2,2,7}G capped selenoprotein mRNAs are translated *in vivo* but not efficiently recognized by the canonical initiation factor eIF4E. We showed that this cap hypermethylation is performed by the trimethylguanosine synthase 1 (Tgs1) that is recruited by the ubiquitous Survival of MotoNeurons (SMN) protein, involved in spinal muscular atrophy. SMN is part of a chaperone complex that collaborates with the methylosome for RNP assembly.

By ribonucleoprotein immunoprecipitations (RNP IP), we showed that the SMN complex and the methylosome interact with SBP2 *in vivo*. We analysed the role of individual SMN and methylosome components in selenoprotein mRNP assembly and translation. SBP2 interacts directly with 4 proteins of the SMN complex and the methylosome core proteins. The SBP2/methylosome complex could be reconstituted using baculovirus expression. Nevertheless, we showed that SBP2 is not a methylation substrate of the methylosome. We found that both SMN and methylosome complexes are required for efficient translation of the selenoprotein GPx1 *in vivo*. Furthermore we established that the steady-state level of several selenoprotein mRNAs, major regulators of oxidative stress damage in neurons, is specifically reduced in the spinal cord of SMN-deficient mice and that cap hypermethylation of GPx1 mRNA is affected (Gribling-Burrer *et al.*, 2017). Altogether we identified a new function of the SMN complex and the methylosome in selenoprotein mRNP assembly and expression.

References:

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