RNA structure-dependent and cell type-specific regulation of RAN proteins across CAG repeat expansion

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Repeat associated non-AUG (RAN) translation is observed in a growing number of repeat expansion disorders. Although the mechanisms of RAN translation are not yet fully understood, RAN protein levels are increased by PKR activation and reduced by PKR inhibition. Here we report several additional factors that influence RAN translation. First, we show RAN translation across CAG repeat expansions is modulated by the surrounding flanking sequences, with effects that are frame specific. Second, overexpression of accessory factors eIF4B or eIF4H of the RNA helicase eIF4A reduce polyAla RAN protein levels. Third, overexpression of ADAR1 and ADAR2, which reduces p-PKR levels reduces RAN polyAla levels. In contrast, ADAR3 overexpression results in higher polyAla RAN levels without affecting p-PKR. Finally, we have developed a novel transgenic mouse model that expresses CAG-encoded RAN proteins. These mice show cell-type-specific and region-specific accumulation of polyGln and polySer proteins in the brain. These findings provide additional insight into the mechanisms of RAN translation and potential strategies to block RAN protein production.

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