The hnRNP C proteins contain a nuclear retention sequence that can override nuclear export signals

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Nascent pre-mRNAs associate with the abundant heterogeneous nuclear RNP (hnRNP) proteins and remain associated with them throughout the time they are in the nucleus. The hnRNP proteins can be divided into two groups according to their nucleocytoplasmic transport properties. One group is completely restricted to the nucleus in interphase cells, whereas the other group, although primarily nuclear at steady state, shuttles between the nucleus and the cytoplasm. Nuclear export of the shuttling hnRNP proteins is mediated by nuclear export signals (NESs). Mounting evidence indicates that NES-bearing hnRNP proteins are mediators of mRNA export. The hnRNP C proteins are representative of the nonshuttling group of hnRNP proteins. Here we show that hnRNP C proteins are restricted to the nucleus not because they lack an NES, but because they bear a nuclear retention sequence (NRS) that is capable of overriding NESs. The NRS comprises approximately 78 amino acids and is largely within the auxiliary domain of hnRNP C1. We suggest that the removal of NRS-containing hnRNP proteins from premRNA/mRNA is required for mRNA export from the nucleus and is an essential step in the pathway of gene expression.