

NUCLEAR AND CYTOPLASMIC LOCALIZATION SIGNALS IN PROTEIN 4.1R

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Red blood cell protein 4.1, 4.1R, represents an extreme variation on the theme of isoform multiplicity. The diverse 4.1R isoforms, generated by alternative pre-mRNA splicing, are localized at different intracellular sites. We cloned human lymphoid 4.1R cDNAs to define specific domains involved in differential intracellular targeting of 4.1R. Thirteen 4.1R isoforms were identified, four of them localized to the nucleus and the other nine to the cytoplasm. A comparative analysis of the exon composition of the 4.1R cDNAs cloned and of appropriate composite cDNA constructs with the subcellular distribution of their respective products demonstrated that: 1) a ‘core’ region encoded by constitutive exons had the capacity of localizing to the nucleus and conferred nuclear targeting to a cytosolic reporter; 2) exon 5-encoded sequences eclipsed nuclear entry of the core region and conferred cytoplasmic localization to a nuclear reporter; 3) when exons 5 and 16 were both expressed, the nuclear targeting effect of exon 16 was dominant to the inhibitory effect of exon 5; 4) the N-terminal domain of high molecular weight 4.1R isoforms was dominant over all the signals, being sufficient to abrogate nuclear entry. Taken together, these results indicate that all 4.1R molecules contain a conserved region that is sufficient to target the protein to the nucleus, but that specific exon-encoded sequences modulate this capacity by acting in a hierarchical order.