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New human alpha1 soluble guanylyl cyclase splice variants as potential regulators of sGC activity

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Soluble Guanylyl Cyclase (sGC) is an obligatory heterodimeric protein (α/β), which is activated by Nitric Oxide (NO) and mediates a wide variety of NO physiological functions, including, but not restricted to vasodilation, platelet aggregation and neurotransmission. Four sGC subunits named α_1, α_2, β_1 and β_2, products of four independent genes, have been identified in humans. The α_1/β_1 sGC heterodimer is the main form expressed in various tissues and is regarded as the major isoform mediating vasodilation. We have identified three additional variants of α_1sGC generated by alternative splicing. One α_1 sGC splice form, named N1-type, codes a 363 amino acids protein with fully eliminated catalytic domain due to a 330 amino acid C-terminal deletion. This form also contains a unique stretch of 3 amino acids at the C-terminus. A second type, named N2-type, codes a protein that preserved only 126 N-terminal residues and gained additional 17 unique residues. The third identified splice α1 sGC variant, termed C-type, has a 240 amino acid deletion in the N-terminus, but maintains intact the regulatory and catalytic domains [1,2]. RT-PCR analysis of N1, N2- and C-type α_1 sGC mRNA levels indicates that abundance of these splice forms vary in different human tissues and during differentiation of human embryonic stem cells. These data indicate that expression of these isoforms is independently regulated.

Co-expression of C-type α_1 sGC variant with full length β_1 sGC in Sf9 cells demonstrated that the splice variant heterodimerizes with the β_1 subunit to produce NO-sensitive catalytically active enzyme. N1-type α_1 sGC co-expressed at different ratios with α_1/β_1 sGC in Sf9 cells had dominant negative effects. BE2 human neuroblastoma line was stably transfected to overexpress N1- or C-type α_1 isoforms. NO-dependant cGMP production in these lines was decreased for N1-type and increased for C-type, which corroborates the results obtained in Sf9 cells.

In summary, our data suggest that alternative splicing of the α_1 subunit is a novel mechanism for sGC regulation in different human tissues.

References

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