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Transcriptional regulation of guanylylcyclase/natriuretic peptide receptor-a gene by cooperative interactions of histone acetylases and transacting factors

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Cardiac hormones atrial and Brain Natriuretic Peptides (ANP, BNP) bind and activate Guanylyl Cyclase/Natriuretic Peptide Receptor-A (GC-A/NPRA), which plays critical roles in the regulation of blood pressure and cardiovascular hemostasis. Currently, the mechanisms regulating the transcriptional activation and functional expression of Npr1 gene (coding for GC-A/NPRA) are not well understood. To delineate the transcriptional regulatory mechanisms of Npr1gene, we have studied the interactive roles of All-Trans Retinoic Acid (ATRA), Ets-1, SP-1, and histone acetylase p300. Deletional analysis of Npr1 promoter, luciferase assays, and chromatin immuno precipitation analyses indicated that ATRA was able to enhance Npr1 promoter activity by 8- to 10-fold in a time- and dose-dependent manner. In addition, ATRA remarkably enhanced the Guanylyl Cyclase (GC) activity of the receptor and accumulation of intracellular second messenger cGMP. The chromatin immuno precipitation analysis indicated that ATRA stimulated the binding of both Ets-1 and Sp1 to the Npr1 promoter. The Retinoic Acid Receptor (RAR) was recruited by Ets-1, Sp1, and p300 to form a transcriptional co-activation complex with Npr1 promoter. Moreover, ATRA also increased the acetylation of histones H3 and H4 and enhanced their recruitment to Ets-1 and Sp1 binding sites of Npr1 promoter. Our results have provided direct evidence that ATRA signaling up regulates Npr1 gene transcription stimulates the GC activity and intercellular production of cGMP by activating the recruitment of RAR, Sp1, Ets-1, and p300 complex that binds to Npr1 promoter. The findings of these studies are important for understanding the functional roles of Npr1gene of the possible therapeutic molecular targets in the treatment of high blood pressure and cardiovascular diseases.

Biography

Kailash N Pandey received his PhD in Cell Biology from the University of Kentucky in 1979. He carried out Postdoctoral studies in the Department of Biochemistry at Vanderbilt University and in 1986 was appointed as a faculty member. In 1990 he joined the faculty of the Medical College of Georgia as an Associate Professor in the Department of Biochemistry and Molecular Biology. He joined Tulane in 1997. He has served on the Editorial Board of Endocrinology and reviewed manuscripts for a number of other journals. He has served on AHA, NIH and NSF grant review committees. The long-term objectives of his research projects are to delineate the molecular and cellular action of atrial natriuretic peptide (ANP) hormone, which controls natriuresis, diuresis, cell proliferation, and steroidogenesis. The regulatory action of ANP is mediated by interacting with the guanylylcyclase/natriuretic peptide receptor-A (NPRA) that synthesizes the intracellular second messenger cyclic-GMP. Interaction of ANP with the NPRA plays a central role in the pathophysiology of hypertension and cardiovascular disorders.

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