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DREAM regulates insulin promoter activity through newly identified DRE element

Research Article

Teodora Daneva[1,*], Shina Pashova[1], Radoslava Emilova[2], Plamen Padeshki[3], Hristo Gagov[2], Volodia Georgiev[1]

[1]*Department of Immunobiology of Reproduction, Institute of Biology and Immunology of Reproduction to Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria*

[2]*Department of Human and Animal Physiology, Faculty of Biology, 'St. Kliment Ohridski' University of Sofia, 1164 Sofia, Bulgaria*

[3]*National Center of Infectious and Parasitic Diseases, Microbiology Department, 1504 Sofia, Bulgaria*

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Abstract: Downstream regulatory element antagonist modulator (DREAM) protein is a 31 kDa Ca^{2+}-regulated transcriptional repressor. It functions as a silencer of the gene transcription. In low intracellular free Ca^{2+} concentration DREAM tightly binds to the downstream regulatory element (DRE) of gene promoter and impedes the transcription. In higher Ca^{2+} concentrations DREAM binds Ca^{2+} and disconnects from DRE of the gene promoter enabling transcription. We report that DREAM is expressed in different human tissues including the pancreas, where it is located in the islets of Langerhans. Location of DREAM in RIN-F5 cells in cultures is restricted to the nucleus and membranes and changes after increased Ca^{2+}-levels. The proteins dissociate from dimmers to monomers and translocate out of the nucleus. The expression of DREAM in β-cells in the islets of Langerhans regulates the promoter activity of the insulin gene by directly interacting with the sequence located between +52 bp and +81 bp downstream of the transcriptional start site of the promoter. Our results provide evidence for the existence of DRE sequence in the insulin gene promoter. It is suggested that DREAM is a repressor of insulin gene transcription, whose effect is mediated by direct binding to DRE sequence.

Keywords: *DREAM • Insulin • Gene transcription • Promoter activity • Islets of Langerhans*

1. Introduction

Downstream regulatory element (DRE) is a specific nucleotide sequence located nearby to the transcription start site of a gene promoter [1,2]. DRE is a gene silencer that suppresses the transcription in an orientation-independent manner, when placed downstream from the transcription start site of a heterologous promoter [1,3]. DREAM (downstream responsive element antagonist modulator), also termed KChIP-3 (potassium channel interacting protein-3) or calsenilin, is a multifunctional protein of the DREAM/KChIP subfamily of calcium sensors (KChIP-1 to -4) [1,4]. DREAM, so far has mainly been known to be expressed in the nervous system in particular in sensory neurons where it has a predominantly nuclear localization. Blocking or unblocking of DRE element by binding or releasing of DREAM protein prevents or triggers the gene transcription [1,5]. The DNA-binding properties of DREAM have been shown to play a role in the regulation of genes in the thyroid gland [6], hematopoietic stem/progenitor cells [7], melatonin production in the pineal gland and the retina [8], perception of pain [9] and to control learning and memory [10].

DREAM contains four EF-hands that are helix-loop-helix structural domains, which are present in many Ca^{2+}-binding proteins and three of them have functional importance. In low Ca^{2+} concentrations DREAM remains tightly bound to DRE and thus repress the transcription [4,11,12]. The Ca^{2+}-DREAM interaction induces a

* *E-mail: danevadoki@abv.bg*