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Multiple functions of the histone chaperone Jun dimerization protein 2

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ABSTRACT

The Jun dimerization protein 2 (JDP2) is part of the family of stress-responsible transcription factors such as the activation protein-1, and binds the 12-*O*-tetradecanoylphorbol-13-acetateresponse element and the cAMP response element. It also plays a role as a histone chaperone and participates in diverse processes, such as cell-cycle arrest, cell differentiation, apoptosis, senescence, and metastatic spread, and functions as an oncogene and anti-oncogene, and as a cellular reprogramming factor. However, the molecular mechanisms underlying these multiple functions of JDP2 have not been clarified. This review summarizes the structure and function of JDP2, highlighting the specific role of JDP2 in cellular-stress regulation and prevention.

Contents

Abbreviations: ATF-2, activation transcription factor-2; cAMP, cyclic adenosine monophosphate; ARE, antioxidant-responsive element; AP-1, activation protein-1; bZIP, basic leucine zipper protein; CBP, CREB-binding protein; C/EBP, CAAT enhancer-binding protein; CHOP, C/EBP homologous protein; CRE, cAMP response element; HAT, histone acetyltransferase; HDAC, histone deacetylase; iPSCs, induced pluripotent stem cells; INHAT, inhibition of histone acetyltransferase; JDP2, Jun dimerization protein 2; Keap1, Kelch-like ECH-associated protein 1; MafK, musculoaponeurotic fibrosarcoma oncogene homolog K; MEFs, mouse embryonic fibroblasts; Nrf2, nuclear-factor erythroid 2-related factor 2; PR, progesterone receptor; PRC, polycomb repressive protein complex; RANKL, receptor activator of nuclear-factor kappa-B ligand; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; TRE, TPA response element.

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1. Introduction

The Jun dimerization protein 2 (JDP2) is a member of the activating protein-1 (AP-1) family of transcription factors, detected using the Sos recruitment system, and dimerizes with c-Jun to repress AP-1-mediated activation (Aronheim et al., 1997). Based on a yeast two-hybrid system with the activation transcription factor 2 (ATF2) as bait, it was later shown to repress ATF-mediated transcriptional activation (Jin et al., 2001). The gene that encodes JDP2 is located on human chromosome 14 (Blazek et al., 2003) and is composed of four exons; its transcriptional start site is located in exon 1 and the translational start site is located in exon 2. Although JDP2 is transcribed ubiquitously (Jin et al., 2001), it is predominantly enriched in the mouse lung and brain. The alternative splicing of JDP2 generates at least seven transcripts, including two unprocessed transcripts and five coding transcripts that generate two isoforms. The canonical sequence of JDP2 is 163 amino acids long (molecular weight, 18,704 Da), and isoform 2 contains 174 amino acids, with an extra 11 amino acids located at the amino terminus (molecular weight, 19,783 Da) (Fig. 1). This family is a group of basic leucine zipper (bZIP) proteins (Aronheim et al., 1997; Jin et al., 2001; http://www.ncbi.nlm.nih.gov/gene/122953), that bind the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) response element (TRE) and the cAMP response element (CRE) via heterodimerization with c-Jun or ATF-2 (Aronheim et al., 1997; Jin et al., 2001). JDP2 binds not only to DNA *cis elements*, but also to histones and the nucleosome, indicating that JDP2 possesses histone chaperone activity and inhibition of histone acetyl transferase activity (INHAT) (Jin et al., 2006). JDP2 is involved in multiple and diverse processes. Knockout mice for Jdp2 exhibit a shorter tail and small size, increased cell proliferation and differentiation (Pan et al., 2010), and a lower number of neutrophils and osteoclasts (for bone homeostasis) (Maruyama et al., 2012). Transgenic mice with JDP2 specifically expressed in the heart acquire massive atrial dilatation and lethal phenotype (Kehat et al., 2006). In this review, we focus on the structure and functions of JDP2, such as cell differentiation, apoptosis, cell-cycle arrest, senescence, and antioxidation. Depending on the context, JDP2 displays both oncogenic and tumor-suppressive properties. Recently, JDP2 was shown to play a role in the cellular reprogramming of somatic (Liu et al., 2015) and cancer (Chiou et al., 2013) cells. These functions will be addressed and targeted for future use as therapies in regenerative medicine and aging.

2. JDP2 gene and expression

The human and mouse JDP2 genes are located on chromosome 14q3 and chromosome 12D2, respectively. JDP2 consists of four exons and spans about 46.4 kb and 39 kb, respectively (chr 14: 75,474,111 to 75,427,716; chr 12: 85,599,105 to 85,639,878). Its coding-region products produce a canonical protein of 163 amino acids (Aronheim et al., 1997), one variant of 174 amino acids, and one truncated protein of 134 amino acids that originates from the truncated transcript of the 3′-terminus. The single-nucleotide polymorphism (SNP) of *JDP2* gene that correlates with intracranial aneurysms was detected among Japanese, Korean and Dutch cohorts (Krischek et al., 2010). In the mouse, SL-3-3 MLV-induced T-cell lymphomas show the insertional mutagenesis into the 250 kb locus of Fos/Jdp2/Batf locus (Rasmussen et al., 2005).

Seven transcripts of JDP2 have been identified, two of which are expressed pseudo-transcripts, which do not encode the JDP2 protein. The three transcripts of 5.4, 3.78, and 0.972 kb encoded one canonical JDP2 protein with 163 amino acids, the 1.7 kb transcript encodes a JDP2 spliced protein with 174 amino acids, and the 0.631 kb transcript leads to a truncated JDP2 protein with 134 amino acids and the remaining two transcripts (0.518 kb and 0.454 kb) are not encoding. The expression of JDP2 transcripts seems to be ubiquitous.

3. JDP2 protein structure

3.1. Domain structure

JDP2 belongs to the family of AP-1, which is a member of basic Zipper (bZIP) protein family. It contains a basic region from amino acid residues 74 to 96, and four (or five) zipper regions are located at

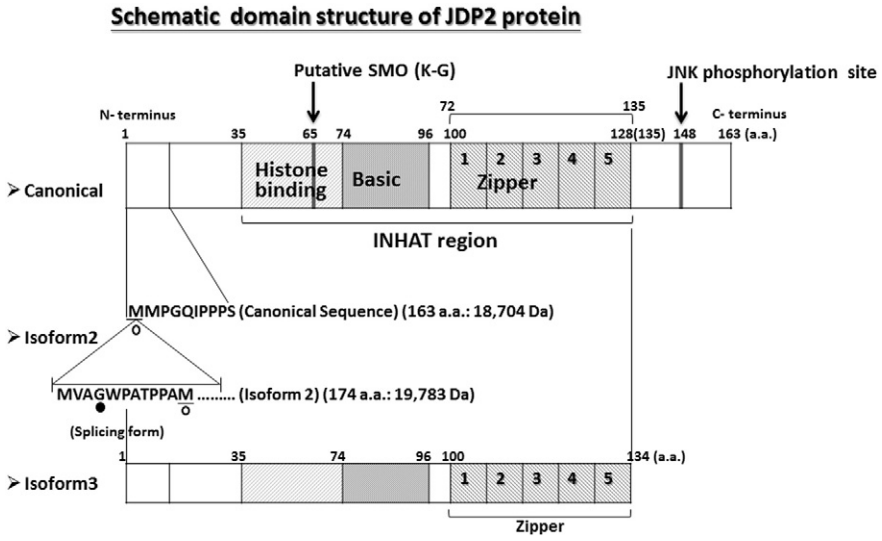

Fig. 1. Schematic domain structure of Jun dimerization protein 2. The models of three Jun dimerization protein 2 (JDP2) isoforms such as canonical protein (163 amino acids) and isoform 2 (174 amino acids) and isoform 3 (134 amino acids) were presented [http://www.ncbi.nlm.nih.gov/gene/122953 LocusLink Report (LocusID: 122953), Aronheim et al., 1997; Jin et al., 2001; Kawaida et al., 2003]. The histone binding, basic region and leucine zipper region were listed (Jin et al., 2006). The first to fourth leucine zipper regions are L–L type and the 5th zipper region is L–H type.