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BHLH Transcription Factors DEC1 and DEC2: From Structure to Various Diseases

Yunyan Wu[1*] & Hiroshi Kijima[1]

[1]*Department of Pathology and Bioscience, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori 036-8562, Japan*

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ABSTRACT

DEC1 and DEC2 genes encode transcription factors which belong to the Hairy/Enhancer of Split subfamily of basic helix-loop-helix (bHLH) factors. The gene expression of DEC2 is regulated in a cell type-specific manner, whereas that of DEC1 is distributed ubiquitously in adult tissues, with the highest expression in cartilage, spleen, lung and intestine. The encoded proteins of DEC1 and DEC2 play vital roles in many biological processes including development, cell differentiation, cell growth, cell death, immune regulations, circadian rhythms, and oncogenesis. Disorder of DEC1 and/or DEC2 in mammalian and the corresponded diseases were discussed here.

Keywords: DEC1/Stra13/SHARP-2; DEC2/mDEC2/SHARP-1; Circadian Rhythm; Hypoxia;

Abbreviations: DEC: Differentiated Embryonic Chondrocyte, bHLH: Basic Helix-Loop-Helix, HIF: Hypoxia Inducible Factor, HRE: Hypoxia Response Element

1. INTRODUCTION

Human DEC1 cDNA was cloned from a human embryo chondrocytes cultured with dibutyryl cyclic AMP [1]. The mouse, rat form were named as the stimulated with retinoic acid 13 (Stra13) [2] and the enhancer of split- and hairy-related protein-2 (SHARP-2) [3], respectively. Human DEC1 consists of 412 amino acid residues, with molecular mass 45510 Da. There is a bHLH domain ranged among 50-111 amino acids in the N-terminal region, an Orange domain from 140-184 amino acids in the central region, as well as a proline-rich domain span 310-385 amino acids in the C-terminal region. Region 1-139 is essential for interaction with ARNT/BMAL1, E-box binding and repressor activity against the CLOCK-ARNT/BMAL1 heterodimer, while region 75-79 is necessary for interaction with retinoid X receptor (RXR) α and repressor activity against RXRα [4]. Fujimoto K et al. cloned human DEC2 by performing 5'- and 3'-RACE (Rapid Amplification of cDNA Ends) with human chondrocyte cDNA [5]. Human DEC2 protein contains 482 amino acids with a molecular weight of 50498 Da. The rat and mouse homologue were named as the enhancer of split- and hairy-related protein-1 (SHARP-1), and mDEC2 and mSHARP-1, respectively [3, 6, 7].

2. Expression of DEC1 and DEC2

The expression of DEC1 and DEC2 is regulated by various extracellular stimuli, such as growth factors [3, 8], hypoxia [9], hormones [10-12], and cytokines [13].

2.1 DNA/RNA expression of DEC1 and DEC2

According to the Entrez-Gene, DEC1 gene maps to NC_000003.12 in the region between 4979412 and 4985181 on the minus strand and spans across 5.7 kilo bases with 5 exons and 4 introns. DEC1 mRNA (NCBI Reference Sequence: NM_003670.2) has 3061 bps. On the other hand, DEC2 gene maps to NC_000012.12 in the region between 26120026 and 26125070 on the minus strand and spans across 5.0 kilo bases and consists of 5 exons and 4 introns. DEC2 mRNA (NM_030762.2) has 3796 bps. Northern blot and RT-PCR analysis showed that the mRNA expression of DEC2 was in a tissue- or cell-type restricted manner. High expression is found in the heart, skeletal muscle, and brain, while low expression is found in the lung, placenta, pancreas [3, 5]. However, DEC1 mRNA ubiquitously distributed in adult tissues [1, 3].

Corresponding Author: Dr. Yunyan Wu, Department of Pathology and Bioscience, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan. Tel: +81-172-39-5029, Fax: +81-172-39-5030. E-mail address: yunyanwu@hirosaki-u.ac.jp

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2.2 Protein expression of DEC1 and DEC2

Protein sequence of DEC1 and DEC2 is not well conserved between mammals; however, the bHLH motif in the N-terminal is highly conserved, that is, the homology of DEC1 and DEC2 in bHLH motif is 97%. While the similarity in the Orange domain is 52%. In addition, the overall homology between the two proteins is 42%.

The bHLH domain, commonly found in many sequence specific DNA-binding proteins, consists of a conserved core of approximately 50 amino acids in a pattern of two amphipathic helices joined by a variable length linker region that could form a loop with an extra basic region about 15 amino acid residues. The HLH domain mediates the homo- or hetero-dimerization which is necessary for DNA binding, and the basic region is required for DNA binding activity. DEC1 and DEC2 recognize and bind to a class B, also known as the canonical E-box sequence, 5'-CACGTG-3' with high affinity. It can also bind variations on the sequence 5'-CANNTG-3' (where N is any nucleotide sequence), but not an N-box with a sequence 5'-CACNAG-3'. The Orange domain present in both DEC1 and DEC2 makes them different from other bHLH family proteins. It is reported to be involved in regulating cell differentiation, embryonic patterning, as well as other biological processes including tumorigenesis and tumor progression [14, 15]. Few studies have discussed the function of Alanine/Glycine-rich domain. However, several researchers speculated that it is the Alanine/Glycine-rich domain that differentiates the role of DEC2 from that of DEC1 in tumorigenesis progress such as regulating apoptosis and epithelial-mesenchymal transitions [16, 17].

3. Functions of DEC1 and DEC2 and relations with disease

The expression of DEC1 and DEC2 is regulated by various extracellular stimuli. The mRNA of DEC2 was induced by NGF (nerve growth factor) in PC12 cells [3]. And many kinds of cytokines can induced the protein and/or mRNA of DEC1 and DEC2, such as TNF-α [18] and IFN-β [13]. In addition, expression of DEC2 is in response to the treatment with polyinosinic-polycytidylic acid (poly-IC), an authentic double-stranded RNA in human mesangial cells [19]. Moreover, DEC1 and DEC2 are reported to be regulated by some anti-cancer drugs, such as paclitaxel and cisplatin, in a cell-specific type [20, 21]. Consequently, these transcription factors play pivotal roles in multiple biological processes including development, cell growth, cell death, oncogenesis, immune system, circadian rhythm, and homeostasis.

3.1 Roles of DEC1 and DEC2 in developmental regulation

DEC1 is expressed in neural system, heart, skeletal muscles, thymus, kidney, and the gastrointestinal tract of the developing mouse embryos. In adult mouse embryos, it is detected in brain, liver, female genital tract, lung, kidney, spleen and heart [2]. DEC1 may transcriptionally repress mesodermal and endodermal differentiation and induce neuronal differentiation in P19 cells [2].

In situ hybridization analysis revealed that DEC2 mRNA is expressed in specific dorsal regions of the developing brain, heart, eye, the olfactory system, limb buds, liver, prevertebrae of the developing mouse embryos [22]. In adult mouse tissues, DEC2 is mainly found in skeletal muscle and brain [5]. Besides, DEC1 and DEC2 participate in mammary gland development in a mutually exclusive manner, that is, DEC1 mRNA is strongly involved in the early stage of involution whereas DEC2 mRNA appeared only during late stages of involution [10].

3.2 Roles of DEC1 and DEC2 in cell differentiation and growth

Both DEC1 and DEC2 participate in the process of cell differentiation and cell growth. The level of DEC1 mRNA is rapidly induced during the differentiation of trophoblast giant cell [2, 23], neuron [2, 3], chondrocyte [1, 8] during mouse embryo development. DEC1 mRNA is also increased at the early stage of 3T3-L1 and 3T3-F442A preadipocytes when treated by adipogenic stimuli [12, 24]. However, the upregulated expression of DEC1 related to the inhibition of preadipocytes differentiation into adipocytes by transcriptionally repressed peroxisome proliferator-activated receptor (PPAR) γ, which is one of the key regulators of adipogenesis [25]. Additionally, DEC1 functioned as one of the transcription factors and is involved in some aspects of the osteogenic differentiation process of mesenchymal stem cells (MSC), although DEC1 alone cannot induce the whole osteogenic differentiation program [26].

In vitro experiment indicated that co-expression of DEC2 and MyoD blocked the differentiation of C2C12 myoblast cells and C3H10T1/2 into myotube cells [7, 27]. DEC2 interrupted the MyoD-dependent transcription stimulation of differentiation-specific marker genes such as myogenin, MEF2C, and myosin heavy chain by protein-protein interaction with MyoD [27]. Small ubiquitin-like modifier (SUMO) modification of the transcription factor DEC2 is required for its full transcriptional repression activity and function as an inhibitor of skeletal muscle differentiation. DEC2 is modified by sumoylation at two conserved lysine residues 240 and 255. Mutation of these SUMO acceptor sites in DEC2 attenuates its ability to act as a transcriptional repressor and inhibit myogenic differentiation [28].

3.3 Roles of DEC1 and DEC2 in circadian rhythms

Circadian rhythms, about 24 h-cycle rhythms exist in living systems, are generated by a set of genes forming a transcriptional auto-regulatory feedback loop. In mammals, *Clock, Bmal1, Per1, Per2, Cry1, Cry2* genes constitute this feedback loop. The suprachiasmatic nucleus (SCN) of the hypothalamus is identified as the dominant circadian

pacemaker driving rhythms in activity and rest, feeding, body temperature and hormones of mammals [29]. The existence of peripheral clocks has been reported in the liver, kidney, lung and other organs [30-32]. *Dec1* and *Dec2*, described by Honma S, *et al*. as members of the fifth clock-gene family, repress Clock/Bmal1-induced transactivation of the mouse Per 1 promoter through protein-protein interaction with Bmal1 [33]. They expressed higher during the day and this circadian pattern cannot be changed under conditions of constant darkness. DEC1 shows robust circadian expression in the SCN as well as in various peripheral tissues [33-38]. However, the expression pattern of DEC1 and DEC2 in peripheral tissues differs from that of SCN [38]. In the SCN, the expression of both DEC1 and DEC2 mRNA exhibited a peak in the subjective day [33], while in the peripheral tissues, the higher expression is appeared during the subjective night [38].

3.4 Roles of DEC1 and DEC2 in hypoxia treatment

The expression of DEC1 and DEC2 mRNAs is upregulated by hypoxia [9, 25, 39-41]. Functional hypoxia response elements (HRE) are identified in the transcriptional regulatory region of both DEC1 and DEC2. It exists at the nucleotide sequences between -462 and -446 (5'-GGCCAGACGTGCCTGGA-3') of human *DEC1* gene, and localizes between -311 and -295 (5'-TTCCGCACGTGAGCTGG-3') of human *DEC2* gene [9]. Hypoxia inducible factor (HIF)-1 binds to the HRE element and stimulates the transcription of both *DEC1* and *DEC2* genes, consequently suppressing the expression of their target genes under hypoxic conditions, because they usually work as transcriptional suppressors *in vitro* [6, 42-44]. In addition, DEC2 gene contributes to the hypoxic adaptation among long-term high-altitude residents such as Ethiopian, Andean, and Tibetan populations living at high altitude through affecting target genes from the HIF-1α-DEC2-VEGF pathway [45]. On the other hand, hypoxia-mediated changes in circadian rhythms have been suggested to be a key driver of the sleep fragmentation and poor sleep quality seen in lowlanders at high altitude. DEC2 may provide insights into the crosstalk between hypoxia and circadian clock [45]. Pathologically, hypoxic conditions are often present in the inner of most solid tumors. It has been reported that lower DEC2 mRNA level were detected in colon carcinoma tissue than in the adjacent normal tissue which probably caused by the strong expression of DEC1 in the carcinoma cells [46]. Since the expression of DEC2 was inhibited by DEC1 through binding to the E-box which located in its promoter region [46].

3.5 Function of DEC1 and DEC2 in cancer

Abnormal expression of DEC1 and DEC2 is found to be related to various kinds of malignant tumors generally because their roles in cell proliferation, apoptosis, hypoxia responses. Montagner *et al*. showed that DEC2 is a crucial regulator of the invasive and metastatic phenotype in triple-negative breast cancer (TNBC), one of the most aggressive types of breast cancer [47]. DEC2 is upregulated by the p63 metastasis suppressor and inhibits TNBC aggressiveness through inhibition of HIF1α and HIF2α as well as their target genes. DEC2 opposes HIF-dependent TNBC cell migration *in vitro*, and invasive or metastatic behaviors *in vivo*. Mechanistically, DEC2 binds to HIFs and promotes HIF proteasomal degradation by serving as the HIF-presenting factor to the proteasome. This process is independent of the VHL (Von Hippel-Lindau) tumor suppressor, hypoxia, and the ubiquitination machinery. DEC2 therefore determines the intrinsic instability of HIF proteins to act in parallel to, and cooperate with, oxygen levels.

3.6 Mutation of *DEC2* gene results in short sleep

In a mother and daughter with the short sleep phenotype, He *et al*. identified a heterozygous C-to-G transversion in the DEC2 gene, resulting in a pro384-to-arg (P384R) substitution in a highly conserved region within a proline-rich domain close to the C terminus [48]. Both individuals showed normal sleep-onset times, but much earlier sleep-offset time (time of awakening) compared to family members and age-matched controls. The short sleeper phenotype or trait is not considered a sleep disorder. Individuals with this trait require less sleep in any 24-hour period than is typical for their age group. In vitro functional expression studies showed that the P384R protein attenuated Dec2 repressive activity of Clock /Bmal1-induced transactivation. Transgenic mice carrying the heterozygous P384R mutation showed increased vigilance time and less sleep time than control mice.

4. CONCLUSIONS

We reviewed our current understanding of the bHLH transcription factors DEC1 and DEC2, including structures, functions, as well as their roles in various diseases. Recently reports show that not only normal cells but also cancer cells own their rhythms in gene expression. This phenomenon has been used in cancer therapy known as chronotherapy. The multiple roles of DEC1 and DEC2 in development, differentiation, and pathology as well as their functions in circadian rhythm reveal the value of further understanding of their functions.

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