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Mammalian HECT ubiquitin-protein ligases: Biological and pathophysiological aspects ☆

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ABSTRACT

Members of the HECT family of E3 ubiquitin-protein ligases are characterized by a C-terminal HECT domain that catalyzes the covalent attachment of ubiquitin to substrate proteins and by N-terminal extensions of variable length and domain architecture that determine the substrate spectrum of a respective HECT E3. Since their discovery in 1995, it has become clear that deregulation of distinct HECT E3s plays an eminent role in human disease or disease-related processes including cancer, cardiovascular and neurological disorders, viral infections, and immune response. Thus, a detailed understanding of the structure–function aspects of HECT E3s as well as the identification and characterization of the substrates and regulators of HECT E3s is critical in developing new approaches in the treatment of respective diseases. In this review, we summarize what is currently known about mammalian HECT E3s, with a focus on their biological functions and roles in pathophysiology. This article is part of a Special Issue entitled: Ubiquitin–Proteasome System.

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1. Introduction

Covalent attachment of ubiquitin to proteins ("ubiquitination") is involved in the control of many, if not all, eukaryotic processes indicating that the recognition of proteins by the ubiquitin-conjugation system must be a highly specific and adjustable process [1,2]. Substrate specificity of the ubiquitin-conjugation system is mainly mediated by E3 ubiquitin-protein ligases that constitute a large class of proteins, with the human genome encoding more than 600 putative E3s or E3 complexes [1–3]. In a simplified view, E3s are characterized by the presence of at least two functional domains/regions. One domain mediates the interaction with the cognate E2 ubiquitin-conjugating enzyme(s), while the other is responsible for the specific recognition of substrate proteins. Based on the identity of the domain involved in E2 interaction, E3 proteins can be grouped into two main families, HECT domain E3s and RING and RING-like (e.g., U-box) domain E3s [3–6]. While the HECT domain is assumed to have an enzymatic activity and to directly catalyze the covalent attachment of ubiquitin to substrate proteins via a ubiquitin–HECT thioester complex intermediate [3–5], most RING/RING-like domains do not appear to have an enzymatic activity but rather act as allosteric activators of E2s [3,6]. Notably, members of the RING-between-RING (RBR) subfamily of RING E3s have recently been shown to act as RING/HECT E3 hybrids: one RING functions as docking site for cognate E2s (UbcH7, UbcH5 family members), while the other RING accepts ubiquitin from the E2 in the form of a thioester complex as an obligatory intermediate step in RBR-mediated ubiquitination [7–10].

HECT E3s were first reported in 1995 and, thus, were the first family of E3s described [11]. Like ubiquitin, HECT E3s are found in all eukaryotic organisms, with the genome of *Saccharomyces cerevisiae* and the human genome encoding 5 and 28 HECT E3s, respectively [4]. Furthermore, although they do not encode ubiquitin, the genomes of some pathogenic bacteria (enterohemorrhagic *Escherichia coli* (EHEC) O157:H7; *Salmonella enterica*) encode HECT domain-like E3s that are injected into host cells and presumably exploit the ubiquitin-conjugation system for bacterial purposes [12–15]. HECT E3s range in size from approximately 80 kDa to more than 500 kDa and are characterized by the HECT domain, a C-terminal region of approximately 350 amino acids in length with significant similarity to the C terminus of E6AP (*H*omologous to *E*6AP *C* Terminus) [4,5,11]. While the HECT domain represents the catalytic domain [11,16], the substrate specificity of HECT E3s is mainly determined by their respective N-terminal extensions (Fig. 1). Based on the presence of distinct amino acid sequence motifs or domains within these N-terminal extensions, human HECT E3s have been grouped into three subfamilies: Nedd4/Nedd4-like E3s, which contain WW domains, HERC (*HE*CT and *R*CC1-like domain) E3s harboring RLDs (*R*CC1-*L*ike *D*omains), and

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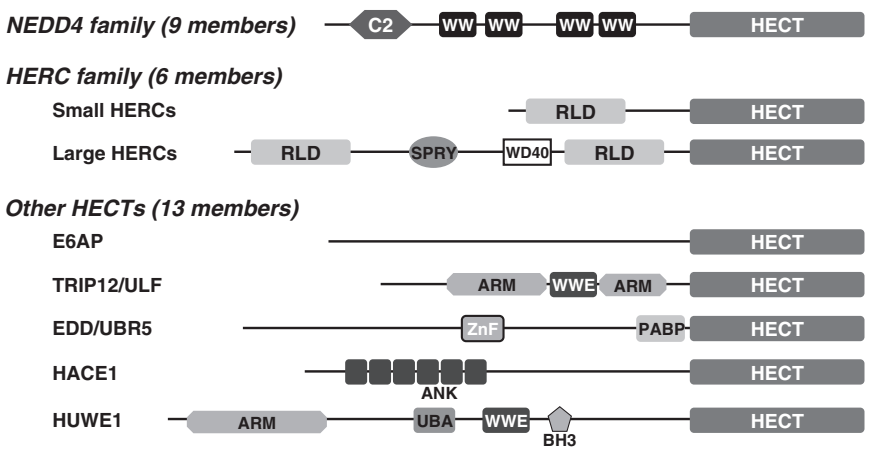

Fig. 1. The human HECT E3 ligases. The human genome encodes 28 members of the HECT E3 family. In all cases, the HECT domain is located at the C terminus of the proteins. The substrate binding is mediated by various domains that are located N-terminal to the HECT domain. The human HECT E3 ligases can be roughly grouped into three families. The NEDD4 family and the HERC family can be readily identified by their distinct domain architectures. NEDD4 members contain an N-terminal C2 domain, 2–4 WW domains and a C-terminal HECT domain. The HERC family members have one or more RCC1-like domains (RLDs). The small HERCs carry a single RLD and large HERCs contain more than one RLD and additional domains. The remaining HECT ligases may contain varied number and types of domains. Schematics are shown for those HECT E3s discussed in this review.

"other" HECT E3s that contain neither RLDs nor WW domains (Fig. 1) [4,5]. Note that this classification is an oversimplification and does not take evolutional considerations into account (for evolutional classification of HECT E3s, see [17]). However, for the sake of convenience, we will use this nomenclature here, when discussing the physiological aspects of selected HECT E3s.

2. Structural and functional aspects of the HECT domain

The HECT domain mediates the interaction with cognate E2s, mainly UbcH7 and members of the UbcH5 subfamily of E2s (for a more comprehensive analysis of the interaction of HECT E3s with E2s, see [18,19]), and forms a thioester complex with ubiquitin via an evolutionally conserved cysteine residue [4,5,11,20]. Since the ability to form ubiquitin thioester complexes in the presence of E2s is necessary for substrate ubiquitination, it is assumed that HECT E3s catalyze the final attachment of ubiquitin to substrate proteins as well as to ubiquitin (in case of ubiquitin chain formation).

2.1. Structure of the HECT domain

Structures of 7 HECT domains (E6AP, WWP1, SMURF2, NEDD4-2/NEDD4L, HUWE1, yeast Rsp5, NEDD4) and the C-terminal portion of the HECT domain of UBR5 have been solved [21–28] (note that structures for full-length HECT E3s are not yet available). The HECT domain adopts a bilobal structure, with the C-terminal lobe containing the catalytic cysteine residue and the N-terminal lobe representing the E2 binding domain. The lobes are linked by a flexible hinge region which presumably facilitates proper positioning of the catalytic cysteine towards the ubiquitin-E2 thioester bond to allow transthioesterification of ubiquitin to the HECT domain: In the absence of ubiquitin, the distance between the catalytic cysteine residue of an unloaded E2 and the catalytic cysteine of the HECT domain is rather large (e.g., ~41 Å in the case of E6AP and ~16 Å in the case of WWP1) [21–23], in fact too large for transthioesterification. The distance appears to be significantly shortened when a ubiquitin-loaded E2 is bound (~8 Å, as shown for the complex between NEDD4-2/NEDD4L and ubiquitin-loaded UbcH5B [24]). Thus, the topology of HECT-E2 complexes depends on the ubiquitin-loading status of the E2 and involves non-covalent interactions between the N lobe and the E2 and ubiquitin and the C lobe [24].

2.2. Regulation of HECT domain activity

The activity of HECT E3s can be regulated at two general levels. One level is the association of an HECT E3 with its substrate protein(s), which in most cases is mediated by specific protein–protein interaction domains/motifs located N-terminal to the HECT domain (Fig. 1). In addition, at least some of the interaction motifs present in HECT E3s bind regulatory proteins that either facilitate ("adaptor and/or auxiliary proteins") or interfere with ("inhibitory proteins") the interaction of substrates with their cognate E3s. For example, Ndfip1 and Ndfip2 as well as several members of the α-arrestin protein family (Arrdc) bind to the WW domains of distinct Nedd4 family members (see 3.1) through PY motifs [29–33], thereby assisting the ubiquitination of respective substrate proteins [5,32,33]. In contrast, binding of 14-3-3 proteins to Nedd4-2, which is regulated by hormone-induced phosphorylation of Nedd4-2 [5,34–36], precludes the interaction of Nedd4-2 with its substrates (e.g., epithelial sodium channel subunits) [5,34,35]. For more detailed discussions of potential mechanisms involved in regulating HECT E3-substrate interaction, see refs. [4,5,37–39].

The other level concerns the catalytic activity of the HECT domain including the interaction with its cognate E2 (for a review, see [37]). Two illustrative examples for the regulation at the HECT domain level are provided by SMURF2 and Itch [23,40,41], both of which are members of the NEDD4-like family of E3s and contain WW domains and an N-terminal C2 domain (Fig. 1). Compared to other HECT domains, the HECT domain of SMURF2 interacts rather ineffectively with its E2 (UbcH7). In fact, for efficient interaction between the HECT domain of SMURF2 and Ubch7 an additional protein – SMAD7 which binds to both the HECT domain of SMURF2 and UbcH7 – is required [23]. Furthermore, NMR studies showed that in the context of full-length SMURF2, the catalytic cysteine of the HECT domain is not accessible for UbcH7, as it is disguised by an intramolecular interaction of the C2 domain with the HECT domain. The inhibitory effect of the C2 domain is also released by SMAD7, the expression of which is regulated by extracellular stimuli (e.g., TGFβ) [40]. With respect to Itch, coprecipitation analyses indicate that the HECT domain interacts with the WW domain rendering Itch inactive. Furthermore, stimulus-dependent phosphorylation of distinct serine and threonine residues in the N terminus of Itch induces a conformational change resulting in the disruption of the WW–HECT domain interaction and, consequently, the activation of Itch activity [41]. Taken together, the activity of at least some HECT domains can be regulated by intra- and/or intermolecular interactions

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