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A short evolutionary journey across the HERC Ubiquitin Ligases

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ABSTRACT

HECT ubiquitin ligases are key components of the eukaryotic ubiquitin-proteasome system controlling different cellular physiological aspects as well as the genesis of several human diseases. Among the HECT family, the HERC subfamily members are characterized by having one or more RCC1-like domains, a C-terminal HECT domain and the molecular mass ranging approximately from 120 kDa to 500 kDa. Due to their large size , some of them are refractory to functional characterization. We have recently identified and functionally characterized a novel large HECT member in *Dictyostelium discoideum* that, in many aspects, exhibits structural similarities with the mammalian large HERC1. In the present minireview , we shortly summarize and revise the current phylogenetic history of HERC proteins among the different living organisms.

Introduction

Ubiquitination, which is the covalent ligation of ubiquitin to a substrate protein, is associated with almost every cellular process including signal transduction, DNA damage repair, cell cycle regulation and autophagic clearance. The process involves three sequential steps each of which is catalysed by a different class of enzymes. In the first step the ubiquitin is activated, in an ATP-dependent way, by the ubiquitin activating enzyme (E1). Afterwards the activated ubiquitin is physically transferred to the ubiquitin conjugating enzyme (E2). Finally, E3 ligases carry out the final step in the ubiquitination cascade, catalysing the transfer of ubiquitin from an E2 enzyme to form a covalent bond with a substrate lysine[1] (Figure 1).

Three distinct families of E3 ligases have been identified, which stimulate the ubiquitin transfer either through a direct or an indirect mechanism, named RING (Really Interesting New Gene), HECT (Homologous to the E6AP Carboxyl Terminus) and RBR (Ring Between Ring)[2] .

In human beings RING is the largest family with more than 600 putative members that do not have a direct catalytic role in protein ubiquitination but basically, they act as scaffold facilitating the interaction between E2 and the substrates. In contrast to RING E3 ligases, the HECT and RBR family members catalyse the ubiquitin transfer to the substrate through a two-step reaction: ubiquitin is first transferred to a catalytic cysteine residue on the E3 and then covalently linked to the substrate[3,4]. HECT E3s can either