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Review

Biological functions of hyaluronan and cytokine-inducible deubiquitinating enzymes

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ABSTRACT

The modification of proteins through post-translation and degradation by the ubiquitin–proteasome system plays a pivotal role in a broad array of biological processes. Reversal of this process by deubiquitination is a central step in the maintenance and regulation of cellular homeostasis. It now appears that the regulation of ubiquitin pathways by deubiquitinating enzymes (DUBs) could be used as targets for anticancer therapy. Recent success in inducing apoptosis in cancerous cells by USP17, a cytokine-inducible DUB encoding two hyaluronan binding motifs (HABMs) showing direct interaction with hyaluronan (HA), could prove a promising step in the development of DUBs containing HABMs as agents in anticancer therapeutics. In this review, we summarize the importance of hyaluronan (HA) in cancer, the role played by DUBs in apoptosis, and a possible relationship between DUBs and HA in cancerous cells, suggesting new strategies for applying DUB enzymes as potential anticancer therapeutics.

Contents

1. Introduction . . . 83
2. HA and cancer . . . 85
3. Intracellular HA . . . 85
4. CD44 and cancer . . . 86
5. Hyaluronic acid as a drug-targeting moiety . . . 86
6. HA oligosaccharides as anticancer therapeutics . . . 86
7. Cytokine-inducible deubiquitinating enzymes with HABMs . . . 87
8. Deubiquitinating (DUB) enzymes as anticancer therapeutics . . . 88
9. Conclusions . . . 89
Acknowledgements . . . 89
References . . . 89

1. Introduction

Covalent attachment of ubiquitin (Ub) to proteins is a significant regulatory step in a diverse array of cellular and biological processes, including embryonic development, cell cycle control, transcriptional regulation, immune response, apoptosis, oncogenesis, pre-implantation, and intracellular signaling pathways [1]. These ubiquitin molecules can be attached to their substrates as monomers or as polymers (Fig. 1). In general, a monoubiquitination process is involved in the regulation of diverse cellular processes including DNA repair, receptor endocytosis, vesicle sorting, gene silencing, and signal transduction [2–5]. Polyubiquitination processes are involved both in protein degradation

Abbreviations: DUB, deubiquitinating enzymes; HABMs, hyaluronan binding motifs; HA, hyaluronan; Ub, ubiquitin; UCH, ubiquitin C-terminal hydrolases; USP, ubiquitin-specific processing proteases; JAMM, Jab1/Pab1/MPN domain-containing metalloenzymes; OTU, Otu-domain ubiquitin aldehyde-binding proteins; ECM, extracellular matrix; GAGs, glycosaminoglycans; Has, hyaluronan synthesizing enzymes; HYAL, hyaluronidases; SPAM-1, sperm adhesion molecule 1; DOX, doxorubicin; HAUSP, herpes virus-associated ubiquitin-specific protease

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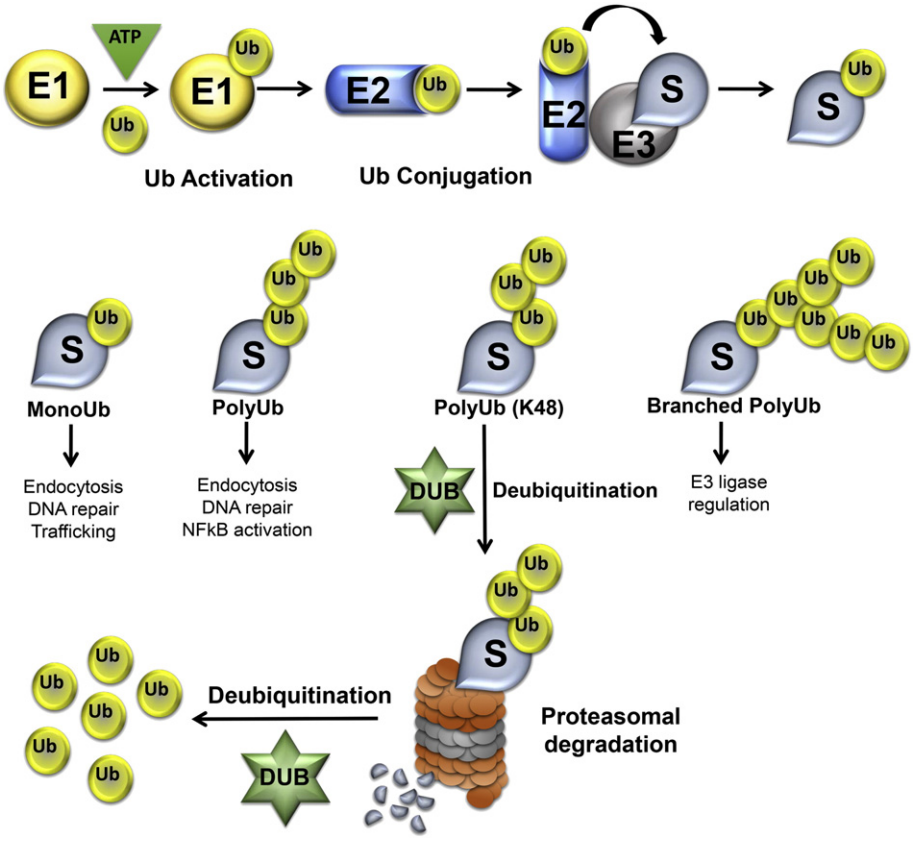

Fig. 1. The ubiquitin proteolytic pathway. The process of ubiquitination is regulated by an organized milieu of E1, E2 and E3 enzymes to mediate the ligation of ubiquitin to the lysine residues in the proteins targeted to the 26S proteasome for degradation. Ubiquitins are recycled by the action of DUB enzymes.

and signal transduction. Ubiquitin itself contains seven Lys residues, comprising K6, K11, K27, K29, K33, K48, and K63 [6], which serve as acceptor sites for other ubiquitin molecules during the formation of ubiquitin chains. Ubiquitin chains are arranged in several different ways. A conjugation of ubiquitin chains linked through lysine 48 serves primarily as a targeting signal for proteasomal degradation by sequential enzymatic actions via ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). A novel ubiquitination factor (E4), required for efficient multiubiquitination, has been identified in yeast [7–9]. K29- and K33-branched ubiquitin chains have been noted in the regulation of AMP-activated protein kinase-related kinases [10]. Recent studies have identified K33 linkages that can restrict T cell receptor (TCR) signaling by disengaging TCR-zeta in T cells [11]. K29-branched ubiquitin chains have also been shown to promote their substrates for proteasomal and lysosomal degradation [12,13]. K63-branched ubiquitin chains are not involved in the protein degradation process. Instead, they are involved in several cellular processes, such as DNA repair, signal transduction, intracellular trafficking of membrane proteins, endocytosis, and stress responses [14–17]. As a result, depending on the cellular function, proteins can be monoubiquitinated, multiubiquitinated, or polyubiquitinated (Fig. 1).

Deubiquitination is a critical step in the regulation of the proteasomal pathway. Deubiquitinating (DUB) enzymes, a large family of proteases, have primarily been instrumental in the renewal of the polyubiquitin chains for use during ubiquitination (Fig. 1). Almost 100 DUB enzyme genes have been identified from the human genome; these enzyme genes are mainly involved in recycling monomeric Ub, the release of Ub from Ub fusion precursors, inverse regulatory ubiquitination, and the editing of inappropriately ubiquitinated proteins [1,18]. Most DUB enzymes are cysteine proteases, which are classified into at least five families: the ubiquitin C-terminal hydrolases (UCH), the ubiquitin-specific processing proteases (USP), Jab1/Pab1/MPN domain-containing metallo-enzymes (JAMM), Otu-domain ubiquitin aldehyde-binding proteins (OTU), and Ataxin-3/Josephin [1,9,19,20].

A relatively recent upsurge in knowledge relating to DUB enzymes (including USP2, USP7, USP8, USP9X, USP15, USP16, USP17, USP28, USP41, CYLD, UCHL-1, Ataxin-2, Ataxin-3, and Ataxin-7) has highlighted their essential roles in promoting apoptosis in cells [21–23]. These DUBs mainly regulate the process between prosurvival signaling and cell death signaling. During cell stresses, such as DNA damage, unfolded protein, and oxidative stress signaling, the expression level of DUBs is either up- or down-regulated, leading to cell apoptosis. In addition, there are several DUBs, namely, DUB-1, DUB-1A, DUB-2, and DUB-2A, which belong to cytokine-inducible DUB subfamily members involved in the regulation of cell proliferation and apoptosis in lymphocytes [9,20]. Recently, we isolated cytokine-inducible DUB USP17 from chorionic villi tissue and various cancer cell lines [24] that induce apoptosis and the death of cancerous cells by negatively regulating histone deacetylases (HDAC) activity [24–26]. USP17, with two putative hyaluronan binding motifs (HABMs), directly interacts with hyaluronan (HA) to inhibit cell proliferation and anchorage-independent tumor growth [27].

An important connective tissue glycosaminoglycan, HA is enriched in pericellular matrices surrounding proliferating and migrating cells. Elevated HA biosynthesis is a common feature in many types of human cancers, and its constitutive interactions with tumor cells have a major influence on tumor growth and metastasis, promoting anchorage-independent growth and invasiveness in animal models [28–30]. Apart from its significant role in the extracellular matrix (ECM), HA can also be detected in the rough endoplasmic membrane, plasma membranes, cytoplasm and nuclei of cells in a number of tissues in vivo [31–34]. Intracellular HA tends to accumulate in the perinuclear region of the aortic smooth muscle cells during the premitotic and mitotic stages and facilitates the process of nuclei separation and subsequent cell