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When hypoxia signalling meets the ubiquitin-proteasomal pathway, new targets for cancer therapy

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Abstract

The ubiquitin-proteasomal pathway of degradation of proteins is activated or repressed in response to a number of environmental stresses and thereby plays an essential role in cell function and survival. Hypoxic stress, resulting from a decrease in the concentration of oxygen in tissues, is encountered in both physiological and pathological situations, in particular in cancer. The transcriptional complex hypoxia-inducible factor (HIF) is the key player in the signalling pathway that controls the hypoxic response of mammalian cells. Under hypoxic conditions it transactivates an impressive number of genes involved in a multitude of cellular functions. Tight regulation of this response in part involves the ubiquitin-proteasomal system where oxygen-dependent prolyl-4-hydroxylation of the α subunit of HIF triggers a cascade of events that leads to its degradation by the 26S proteasome. Inhibition of the proteasome in conjunction with topoisomerase inhibition has shown some promise in the treatment of experimental cancer. Such treatment may impact on the hypoxic adaptation of tumour cells.
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Keywords: Hypoxia; Hypoxia-inducible factor-1; Post-translational modification; Prolyl hydroxylase domain protein; Proteasome; SUMO; Ubiquitin; von Hippel-Lindau; Cancer

Abbreviations: ARD1, arrest defective-1 protein; ARNT, aryl hydrocarbon receptor nuclear translocator; bHLH, basic helix loop helix; CBP, CREB binding protein; CPT, camptothecin; C-TAD, C-terminal transactivation domain; FIH-1, factor inhibiting HIF-1; HAT, histone acetyltransferase; HDAC, histone deacetylase; HIF-1, hypoxia-inducible factor-1; MAPK, mitogen-activated protein kinase; MDM2, murine double minute 2; N-TAD, N-terminal transactivation domain; ODDD, oxygen-dependent degradation domain; PAS, PER–ARNT–SIM; PHD, prolyl hydroxylase domain protein; SUMO, small ubiquitin-like modifier; TPT, topotecan; pVHL, von Hippel-Lindau protein.

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1. Introduction

It is well accepted that the activation or repression of the function of proteins is often regulated in response to environmental stimuli by the reversible covalent attachment of chemical groups such as phosphate or acetyl. These post-translational modifications influence protein–protein interactions or stability that in turn modify activity. Polypeptides such as ubiquitin may also be covalently attached to proteins. Early studies indicated that ubiquitin modification concerned essentially misfolded proteins eliminated by degradation by the 26S proteasome. However, it is becoming more and more evident that ubiquitination plays an important role in multiple cell functions, in particular, in cell growth (for review, see [1–3]). For example, ubiquitination regulates the activity of: the p53 tumour suppressor, the inflammatory response mediated by NF-κB, numerous regulators of cell-cycle progression, proteins regulating apoptosis and the transcription factor the hypoxia-inducible factor (HIF). The latter factor is responsible for the induction under hypoxia, low oxygen concentrations, of over 70 genes [4]. Tissue hypoxia occurs during development, wound healing, ischemic disorders and cancer. In the case of cancer, the tumour rapidly outgrows its supply of nutrition and oxygen. To rectify this situation the tumour secretes a number of factors that encourage blood vessel development around the tumour. The upregulation of these secreted factors is dependent on HIF transactivation. The HIF complex is composed of a constitutively expressed β subunit and an α subunit that is rapidly degraded under normoxic conditions (21% O_2) but stable under hypoxic conditions. The stability and subsequent transactivation function of the α subunit of HIF is regulated by its post-translational modification, in particular hydroxylation and phosphorylation (for review, see [5]). It has been shown that hydroxylation of HIF-α on two proline residues by proly-4-hydroxylases is the signal for interaction with the E3 ubiquitin ligase, von Hippel-Lindau protein (pVHL) and subsequent polyubiquitination and degradation of HIF-α by the proteasomal system (for review, see [6,7]).

1.1. Polyubiquitination and protein degradation by the proteasomal machinery

Ubiquitin, a globular polypeptide of 76-amino acids, is highly conserved in eukaryotes and generally covalently attached to lysine residues in target proteins. Ubiquitination of a substrate requires stepwise catalytic ATP-dependent activation (E1), conjugation (E2) and ligation (E3) (Fig. 1). The existence of a substantial number of E3 ligases suggests that they function in selection of the target protein. Ubiquitin itself can be modified by ubiquitin following successive rounds of E1–E3 catalysis leading to the formation of polyubiquitin chains. Polyubiquitination of a target protein earmarks the protein for degradation by the 26S proteasome while monoubiquitination plays multiple non-degradative roles [3]. The 26S proteasome is a barrel-shaped multiprotein, proteolytic complex made up of a 20S and two 19S regulatory subunits (Fig. 2). The 19S subunit recognizes polyubiquitin chains and de-ubiquitinates the substrate releasing ubiquitin prior to protein degradation. The target protein is then unfolded as it progresses into the channel of the 20S subunit and thereby cannot escape proteolytic cleavage by trypsin-, chymotrypsin- and post-glutamyl peptide-like hydrolase activities of the 20S subunit. Thus, as the protein target feeds into the cylinder endoproteolytic or terminal proteolysis occurs and generates multiple peptides [8].

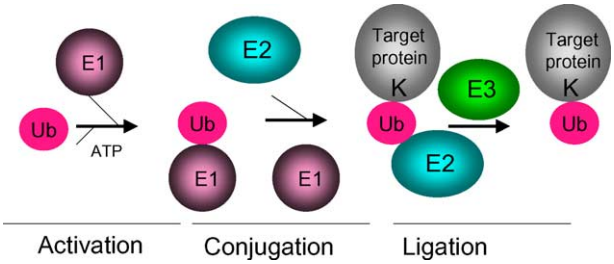

Fig. 1. Cascade for ubiquitination of a target protein. In general ubiquitination of a target protein involves an E1 ubiquitin enzyme activation step that is dependent on ATP, an E2 conjugation enzyme and transfer of ubiquitin to a lysine residue by an E3 ubiquitin ligase. A multiunbiquitin chain-assembly factor (E4) is sometimes required. The reaction is reversible and involves deubiquitin enzymes.

1.2. Ubiquitin-proteasomal regulation of the hypoxia-inducible factor

The HIF complex is a heterodimer of α and β subunit proteins that belong to the basic helix-loop-helix (bHLH)-PAS (PER–ARNT–SIM) family of proteins (Fig. 3). The bHLH and PAS motifs are required for dimerisation while the downstream basic region affords specific binding to the

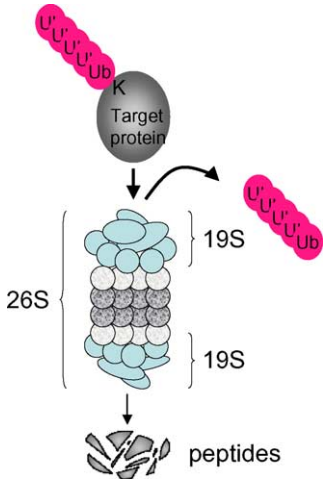

Fig. 2. Proteasomal degradation of a protein earmarked with a polyubiquitin chain. The 26S proteasome consists of a 20S multiprotein core proteolytic complex and two 19S regulatory complexes. The latter binds polyubiquitin chains, which are cleaved for recycling prior to internalization of the target protein, unfolds the target protein in an energy dependent manner and feeds it into the proteolytic chamber which degrades it to produce peptides.

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