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Review

Cellular Functions of Optineurin in Health and Disease

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Optineurin (OPTN) was initially identified as a regulator of NF-κB and interferon signaling, but attracted most attention because of its association with various human disorders such as glaucoma, Paget disease of bone, and amyotrophic lateral sclerosis. Importantly, OPTN has recently been identified as an autophagy receptor important for the autophagic removal of pathogens, damaged mitochondria, and protein aggregates. This activity is most likely compromised in patients carrying OPTN mutations, and contributes to the observed phenotypes. In this review we summarize recent studies describing the molecular mechanisms by which OPTN controls immunity and autophagy, and discuss these findings in the context of several diseases that have been associated with OPTN (mal)function.

The Structure and Characteristics of OPTN Are Key to Its Many Functions

OPTN was first isolated and identified in 1998 in a yeast two-hybrid screen as a binding partner of an adenovirus E3 14.7 kDa protein (E3-14.7K) [1]. In 2002, mutations in the *OPTN* gene were identified in individuals with inherited primary open-angle glaucoma, a major cause of blindness [2], leading to the final name optineurin (for 'optic neuropathy inducing').

OPTN is expressed in most tissues and cells, and its expression can be further enhanced by TNF and interferons [1–3]. The human gene is located at chromosome 10p13, and contains three non-coding exons at its 5′ untranslated region (UTR) and 13 exons that encode a 66 kDa protein. Alternative splicing at the 5′-UTR gives rise to four different isoforms with the same open reading frame, and that encode OPTN variants that probably have different tissue-specific expression patterns [2,4,5]. The mouse *Optn* gene is located at chromosome 2 in a region with high synteny with the human chromosome 10p [5]. Mouse OPTN shows 78% sequence similarity to the human protein, and is also encoded by 13 exons, generating a full-length protein of similar size. Alternative splicing can generate five different isoforms [5]. OPTN is a multidomain protein mediating several functions by interacting with many different proteins. It contains multiple coiled-coil motifs, a basic leucine-zipper motif (bZIP), a microtubule-associated protein 1 light chain LC3-interacting region (LIR), a ubiquitin-binding domain (UBAN), and a C-terminal zinc-finger domain (Figure 1). In addition, OPTN can undergo post-translational modifications, such as ubiquitination and phosphorylation, which affect its function and downstream signaling [6] (Figure 2).

Throughout almost 20 years of studies, OPTN has been implicated in many signaling pathways and cellular processes, but its role in autophagy in particular has attracted attention in recent years. Concurrently, OPTN was found to be associated with several human diseases. We review here the evidence for the different functions of OPTN and examine their association with pathologies.

Trends

OPTN is necessary to mount antiviral IFN type I responses. Genetic ablation of OPTN or expression of an OPTN mutant defective in ubiquitin binding impairs TBK1 and IRF3 activation, and lowers levels of secreted IFN-β.

Pathogen recognition and elimination through autophagy is mediated by the autophagy receptor OPTN and its upstream kinase TBK1.

OPTN is a primary receptor required for the selective autophagy of damaged mitochondria. This process is also regulated via OPTN phosphorylation by TBK1.

Through association with and subsequent ubiquitination by the E3 ligase HACE1, OPTN can bind to the autophagy receptor SQSTM1/p62 and regulate autophagy flux. This ubiquitination event also leads to the proteasomal degradation of OPTN.

Mutations in the *OPTN* gene have been identified in patients suffering from Paget disease of bone and in neurodegenerative diseases including glaucoma, amyotrophic lateral sclerosis, and frontotemporal dementia.

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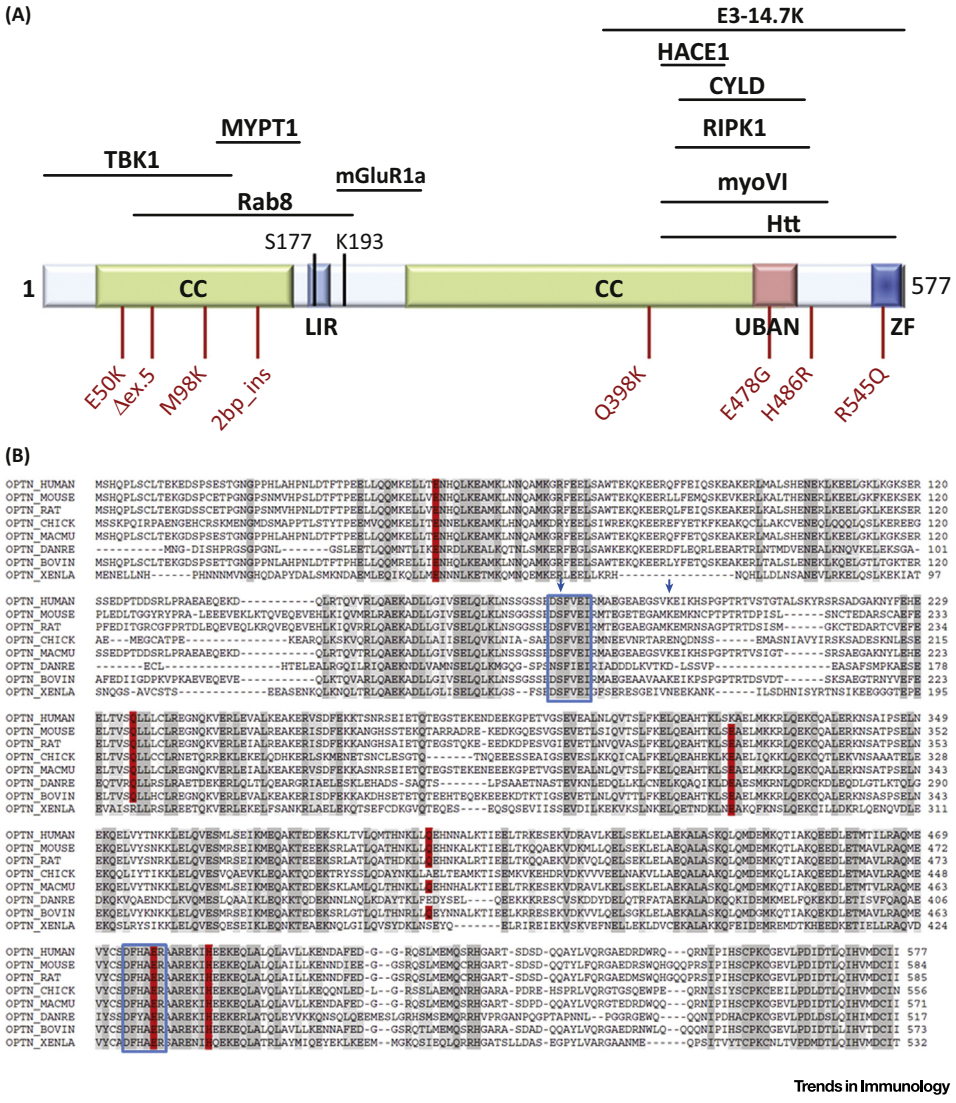

Figure 1. Domain Structure and Interaction Partners of Human Optineurin (OPTN). (A) Schematic representation of OPTN protein domains and known sites of interaction with binding partners. OPTN is a multidomain protein which exerts its multiple functions by interacting with different proteins. S177, phosphorylation site; K193, ubiquitination site. In red: sites of commonly reported mutations, as listed in Table 1. CC, coiled-coil; CYLD, cylindromatosis; E3-14.7K, early region 3 14.7 kDa protein; HACE1, HECT domain and ankyrin repeat-containing, E3 ubiquitin protein ligase 1; Htt, huntingtin; LIR, LC3-interacting region; MYPT1, myosin phosphatase target subunit 1; myoVI, myosin VI; RIPK1, receptor interacting serine/threonine kinase 1; TBK1, TANK-binding kinase 1; UBAN; ubiquitin-binding domain; ZF, zinc finger. (B) Sequence alignment of OPTN proteins from human, mouse, rat, chicken, rhesus macaque (*Macaca mulatta*), zebrafish (*Danio rerio*), bovine, and frog (*Xenopus laevis*), generated using Clustal Omega software. Similarity between species is indicated by grey boxes; conserved mutations associated with human disease are indicated by red boxes; conserved LIR (LC3-interacting region) and UBAN (ubiquitin-binding domain) motifs are indicated by blue boxes; the S177 phosphorylation site and the K193 ubiquitination site are indicated by blue arrows.

OPTN in Cellular Signaling

OPTN in NF-κB Signaling

Because of its strong homology to the nuclear factor-κB (NF-κB) essential modulator, NEMO, the core element of the inhibitor of NF-κB kinase (IKK) complex that is essential for NF-κB activation (Box 1), OPTN was thought to be important for NF-κB signaling (Figure 2). OPTN was shown to act as a negative regulator of TNF-induced NF-κB activation by competing with NEMO