Protein ubiquitination and its role on gene expression during the antiviral immune response

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OBJECTIVES

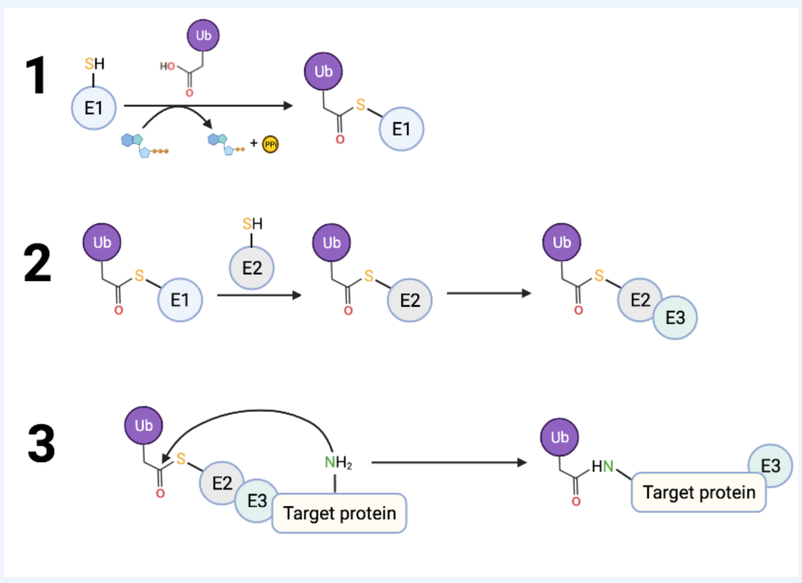
-Define the molecular mechanisms and functions of atypical ubiquitin linkages.

-Describe the role of ubiquitin as a post-translational modification during the antiviral immune response.

-Outline the importance of accurate coordination of the E3 ubiquitin ligase enzymes.

INTRODUCTION

THREE-STEP UBIQUITINATION REACTION



A:The E1-activating enzyme forms an intermediate thioester bond between its Cys and the Ub C-t, which activates the ubiquitin molecule in an ATP-dependent way.

B:The E1 enzyme attaches to the E2-conjugating enzyme. which accepts Ub at a catalytic Cys residue.

C:In conjunction with E2, the E3 ubiquitin ligase enables the transfer of the ubiquitin moiety to the substrate protein by creating an isopeptide bond, generally between a Lys in the substrate and the ubiquitin molecule's C-terminal Gly[1].

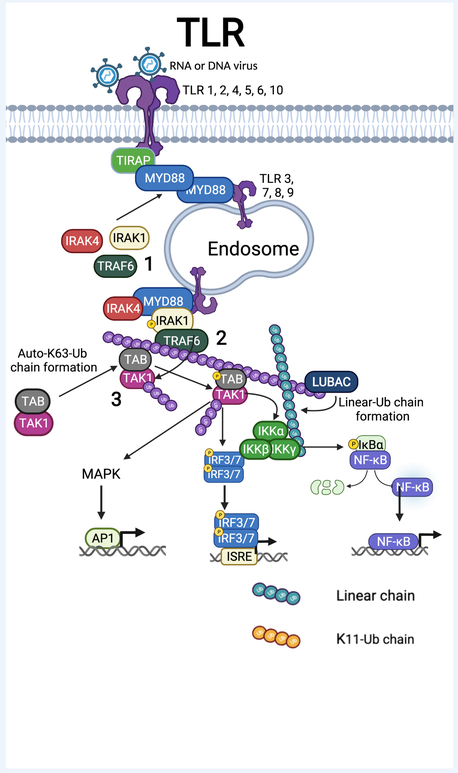
FUNCTIONS OF UBIQUITIN LINKAGES

Ubiquitination	Functions
Monoubiquitination	Gene expression regulation, endocytosis, and DNA damage and replication.
Linear chain	Immune signaling, cell death regulation, and protein quality control.
K6-linked Ub chain	Autophagy and DNA repair
K11-linked Ub chain	Cell cycle regulation, membrane protein trafficking, and TNF signaling.
K27-linked Ub chain	Mitophagy, antiviral immune response, and T cell development.
K29-linked Ub chain	AMPK regulation.
K33-linked Ub chain	AMPK regulation and TCR signaling
K48-linked Ub chain	Proteasomal degradation.
K63-linked Ub chain	DNA repair, kinase activation, protein trafficking and internalization, and signal transduction

A vast number of proteins can recognize ubiquitination.

Distinct proteins recognize different linkages through the ubiquitin-binding domains (UBDs), which leads to specific responses[1,2].

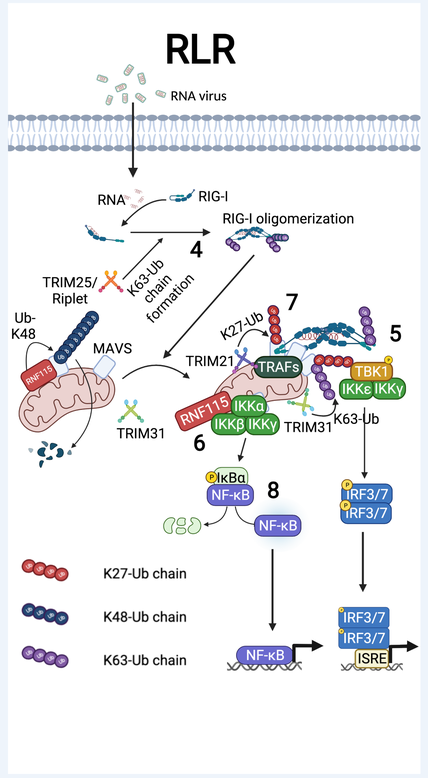
INNATE ANTIVIRAL IMMUNE RESPONSE



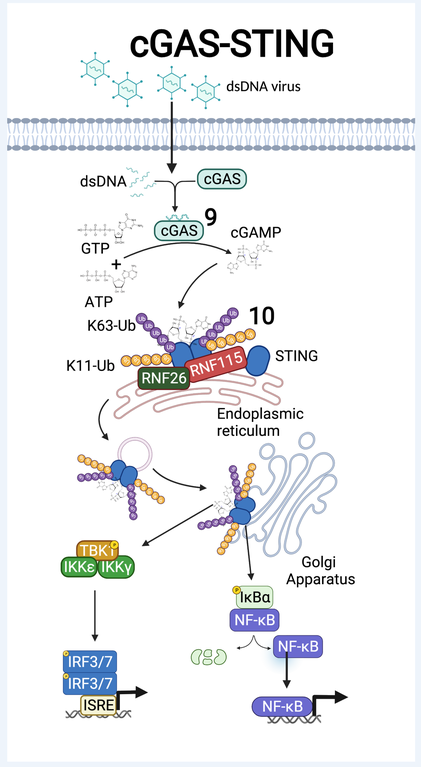
Toll-like receptors recognize PAMPs present in viruses and recruit the scaffold protein Myd88.

Myddosoma formation allows IRAK1 activation (**1**), which associates with the E3 enzyme TRAF6 and catalyzes auto-Ub-K63
chain formation (**2**).

TAK1 binds through its UBD ZNF to the K63-Ub chain, which enables its autophosphorylation (**3**), inducing AP1, NF-κB, and IRF3/7 activation[3].



Upon RNA virus infection, RIG-I changes conformation. Different E3 ligase enzymes target the active conformation of RIG-I and catalyze K63-Ub chain formation at several sites (**4**). RIG-I ubiquitination promotes its polymerization through CARD domains, which induce MAVS recognition in the mitochondria.
MAVS adopts an active prion-like conformation (**7**) needed for TRAFs recruitment. TRAF proteins activate IRF3/7 through TBK1/IKKε/NEMO (**5**) and NF-κB through the IKK complex activation (**6**, **8**)[4].



Viral DNAds is recognized by cGAS (**9**), which catalyzes the transformation of ATP and GTP to cGAMP. The second messenger cGAMP binds to STING, a protein located in the endoplasmic reticulum (**10**).

STING dimerizes and induces vesicle trafficking to the Golgi apparatus, where catalyzed TAK1 phosphorylation, activating AP1, NF-κB, and IRF3/7[3].

UBIQUITINATIONS IN THE ANTIVIRAL IMMUNE RESPONSE

	Target	E3 enzyme	Ubiquitination	Effect
1	IRAK1	TRAF6	K48 chain	Activation
		TRAF6, Pellino 3	K63 chain	Activation/ Inhibition
2	TRAF6	TRAF6	K63 chain	Activation
3	TAK1	TRAF6	K27 chain	Activation
			K63 chain	
4	RIG-I	RNF122, RNF125	K48 chain	Inhibition
		TRIM4, TRIM25, Mex3C	K63 chain	Activation
		Riplet	K63 chain	
5	TBK1	TBK1	K48 chain	Inhibition
		RNF128	K63 chain	Activation
6	IKKγ (NEMO)	TRIM23	K27 chain	Activation
		MARCH2	K48 chain	Inhibition
		TRAF6	K63 chain	Activation
		LUBAC	Linear chain	Activation
7	MAVS	TRIM29	K11 chain	Inhibition
		TRIM21	K27 chain	Activation
		RNF115	K48 chain	Inhibition
		TRIM31	K63 chain	Activation
8	IκBα	$SCF^{\beta\text{-}TrCP}$	K48 chain	Activation
9	cGAS	TRIM56, TRIM41	Monoubiquitination	Activation
		RNF185	K27 chain	Activació
10	STING	RNF26	K11 chain	Activation/ Inhibition
		AMFR/INSIG1	K27 chain	Activation
		RNF5	K48 chain	Inhibition
		TRIM30α		Inhibition
		TRIM29		
		RNF115, TRIM56, TRIM32	K63 chain	Activation

In red: Immune response inhibition; In green: Immune response stimulation; In yellow: Can do both[2,3,4].

CONCLUSIONS

-Ubiquitination is an essential post-translational modification that participates in most cellular processes.

-It plays a crucial role in the antiviral immune response.

-Further studies to describe the underlying mechanisms behind dual ligase enzymes and linkage specificity.

-Clinical relevance: Autoimmune diseases.

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