Mutation Research 769 (2016) 36–46

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

The ubiquitin family meets the Fanconi anemia proteins

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ARTICLE INFO

Article history:
Received 3 May 2016
Accepted 18 June 2016
Available online 23 June 2016

Keywords:
Fanconi anemia
DNA repair
Ubiquitin
NEDD8

ABSTRACT

Fanconi anaemia (FA) is a hereditary disorder characterized by bone marrow failure, developmental defects, predisposition to cancer and chromosomal abnormalities. FA is caused by biallelic mutations that inactivate genes encoding proteins involved in replication stress-associated DNA damage responses. The 20 FANC proteins identified to date constitute the FANC pathway. A key event in this pathway involves the monoubiquitination of the FANCD2-FANCI heterodimer by the collective action of at least 10 different proteins assembled in the FANC core complex. The FANC core complex-mediated monoubiquitination of FANCD2-FANCI is essential to assemble the heterodimer in subnuclear, chromatin-associated, foci and to regulate the process of DNA repair as well as the rescue of stalled replication forks. Several recent works have demonstrated that the activity of the FANC pathway is linked to several other protein post-translational modifications from the ubiquitin-like family, including SUMO and NEDD8. These modifications are related to DNA damage responses but may also affect other cellular functions potentially related to the clinical phenotypes of the syndrome. This review summarizes the interplay between the ubiquitin and ubiquitin-like proteins and the FANC proteins that constitute a major pathway for the surveillance of the genomic integrity and addresses the implications of their interactions in maintaining genome stability.

Contents

1. Introduction

It has been estimated that there are approximately 25,000 genes in the human genome. However, proteome diversity has been estimated to be greater by approximately three orders of magnitude [1]. Diversity can be explained not only by the different isoforms generated from alternative mRNA splicing but also by the enormous number of protein post-translational modifications

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http://dx.doi.org/10.1016/j.mrrev.2016.06.004
1383-5742/

(PTMs) that participate to the maintenance of the cellular homeostasis. Indeed, proteins are generally modified by the covalent addition of several functional groups, such as phosphate groups (phosphorylation), carbonate groups (acetylation, methylation) or nitrate groups (nitrosylation). Proteins are also modified by more complex substrates, such as sugars (glycosylation) or small polypeptides, including ubiquitin and ubiquitin-like molecules (ubiquitination, NEDDylation, SUMOylation, etc.). PTMs have profound effects on protein behaviour by modifying their activity, subcellular localisation, interactions and stability.

The ubiquitin protein is a 76 amino acid polypeptide chain with a molecular weight of 8 kDa that is highly conserved among eukaryotes. This protein can be conjugated to the lysines (K) of target proteins *via* its C-terminal glycine (G). Ubiquitin, being rich in lysines *per se,* is also modified by itself, creating either several branched structures identified by the position of the modified K on the founder ubiquitin (K6, K11, K29, K48, K63) or mixed chains with different combinations [2]. The most described ubiquitin chain is the one occurring on K48 of the ubiquitin, which is then added to a target protein and mediates its degradation via the proteasome complex [3]. A target protein can be modified by the addition of one or several simple and/or branched ubiquitin chains. Therefore, because a protein can undergo simultaneous or sequential addition of one or more mono- or branched-ubiquitin moieties, the regulation of its behaviour by the ubiquitination process is highly complex.

Ubiquitin is the most representative protein of the ubiquitin-like family of proteins that is composed of 9 members: ubiquitin itself and the 8 ubiquitin-like small proteins—NEDD8, ISG15, FAT10, SUMO1 to 4 and ATG12 (Fig. 1A) [2,4–6]. Similarly to ubiquitin, these small proteins are conjugated to a lysine on target proteins. Notably, each member of the family can sequentially target the same lysine on the same protein, adding an additional layer of complexity in the regulation of protein behaviour.

The conjugation process involves a cascade of enzymes that includes an ATP-dependent E1 activating enzyme, an E2 conjugating enzyme and an E3 ligase (Fig. 1A and B). Generally, each targeted K on a protein has its own specific E1, E2 and E3 triad. Finally, specific enzymes (DUBs, deubiquitinases) are devoted to the elimination of the added ubiquitin and ubiquitin-like peptides to fine-tune the regulation of the protein. Defects in protein modification by ubiquitin family members are the cause of or associated with severe human diseases, such as cancer [7,8] and neurodegeneration [9]. Germline mutations altering the ubiquitination pathways or modifying the ubiquitination of target proteins have also been reported in cases of rare genetic syndromes [10].

In this review, we will focus on the crosstalk between the FANC pathway, which is responsible for the human hereditary syndrome Fanconi anaemia (FA), and the ubiquitin and ubiquitin-like family of proteins. To note, the FANC pathway-SUMO interplay has also been extensively presented in a recent review [11].

A

	% ID	E1	E2	E3	DUB
Ubiquitin	100	UBE1 - UBA6	~40	>600	~100
NEDD8	58	NAE1	UBE2M - UBE2F	~10	
ISG15	32-33	UBE1L	UBCH6-UBCH8	HERC5	USP18
FAT10	27-36	UBA6	USE1		
Sumo1	14	SAE1-SAE2	UBC9	~15	SENP1-2
Sumo2	13	SAE1-SAE2	UBC9	~15	SENP1-3-5-7
Sumo3	13	SAE1-SAE2	UBC9	~15	SENP1-3-5-7
Sumo4	12	SAE1-SAE2	UBC9		
ATG12	12	ATG7	ATG10		

B

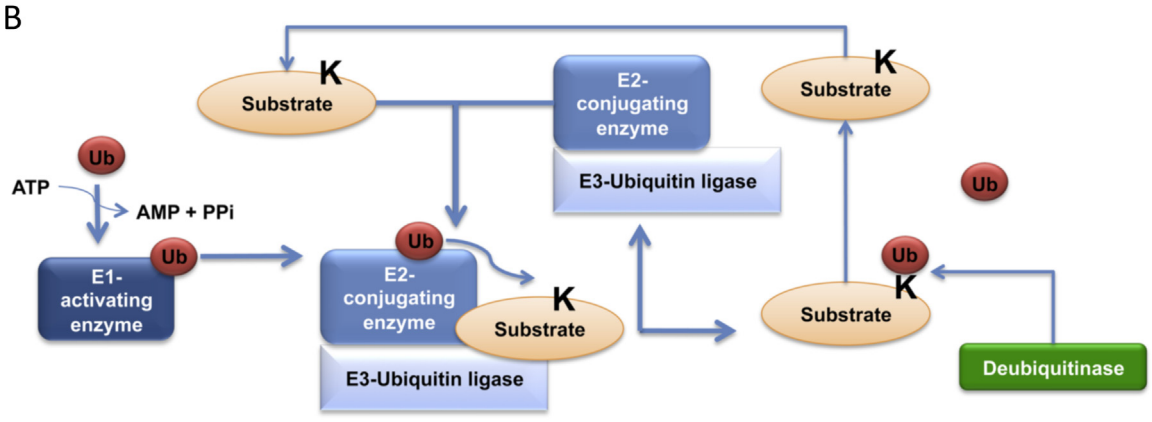

Fig. 1. The ubiquitin family and the conjugation process. A. A table describing the ubiquitin-like family. The percentage of identity compared to ubiquitin is indicated. The number or the name of E1 activating, E2 conjugating, E3 ligase and deubiquitinase (DUB) enzymes is also indicated. B. The ubiquitin conjugation process involves activation of the ubiquitin by the E1 activating enzyme, which is dependent on ATP, leading to the transfer of the ubiquitin to the E2 conjugating enzymes. In association with the E3 ubiquitin ligase, the ubiquitin is linked to the substrate at specific lysine sites. Ubiquitin itself can undergo the same process, leading to the formation of long ubiquitin chains. This process is reversible by the action of specific deubiquitinase enzymes. (Ub: ubiquitin, ATP: adenosine triphosphate, AMP: adenosine monophosphate, PPi: pyrophosphate, K: lysine).