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► **To cite this version:**

Pierre Gâtel, Marc Piechaczyk, Guillaume Bossis. Ubiquitin, SUMO, and Nedd8 as Therapeutic Targets in Cancer. *Proteostasis and Disease*, pp.29-54, 2020, 10.1007/978-3-030-38266-7_2. hal-03014721

HAL Id: hal-03014721

<https://hal.umontpellier.fr/hal-03014721>

Submitted on 1 Dec 2020

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Ubiquitin, SUMO and Nedd8 as therapeutic targets in cancer

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Conflict of interest:

The authors declare no conflict of interest

Abstract

Ubiquitin defines a family of approximately 20 peptidic post-translational modifiers collectively called the Ubiquitin-like (UbLs). They are conjugated to thousands of proteins, modifying their function and fate in many ways. Dysregulation of these modifications has been implicated in a variety of pathologies, in particular cancer. Ubiquitin, SUMO (-1 to -3) and Nedd8 are the best-characterized UbLs. They have been involved in the regulation of the activity and/or the stability of diverse components of various oncogenic or tumor suppressor pathways. Moreover, the dysregulation of enzymes responsible for their conjugation/deconjugation has also been associated with tumorigenesis and cancer resistance to therapies. The UbL system therefore constitutes an attractive target for developing novel anticancer therapeutic strategies. Here, we review the roles and dysregulations of Ubiquitin-, SUMO- and Nedd8 pathways in tumorigenesis, as well as recent advances in the identification of small molecules targeting their conjugating machineries for potential application in the fight against cancer.

Introduction

Ubiquitin is the founding member of a polypeptide family of approximately 20 protein post-translational modifiers [1]. For the sake of simplicity, these, together with Ubiquitin, will be called the Ubiquitin-likes, or UbLs, hereafter. Among them, Ubiquitin, Nedd8 and the 3 members of the SUMO family (SUMO-1 to -3) are at the heart of this review.

UbLs are small globular polypeptides of 8 to 12 kDa. They share low sequence similarity but high structural identity with one α -helix and five β -sheets (β -grasp fold) followed by a C-terminal tail [2]. In most cases, they are covalently conjugated to proteins via formation of an isopeptide bond between their C-terminal glycine and the ϵ -NH₂ group of lysines from substrates. Nevertheless, other, quantitatively minor, conjugations of Ubiquitin to other amino acid residues or at the N-terminus of proteins have been described.

The mechanisms of conjugation are very similar amongst the UbLs even though each one of them is transferred to protein substrates using specific sets of enzymes. Yet, certain of these enzymes can intervene in the conjugation of more than one UbL type under certain conditions (Table 1). As UbL conjugation/deconjugation processes have been described extensively in a number of reviews [3, 4], they will only be addressed briefly below. UbLs are first activated by UbL-activating enzymes called E1s. These use ATP to form a thioester bond between the UbL C-terminal glycine and their catalytic cysteine. The C-terminal glycine is then *trans*-thiolated, allowing the UbL to be transferred onto the catalytic cysteine of UbL-conjugating enzymes called E2s. Although E1s and E2s can, in some cases, be sufficient to conjugate certain UbLs on target proteins, they most often require a third factor called E3 [5, 6]. More than 600 E3s have been proposed for Ubiquitin, but much less for the other UbLs. Certain E3s can be full-blown enzymes. This is the case of the E3 Ubiquitin ligases from the HECT family, which harbor catalytic cysteines forming thioester bonds with the Ubiquitin C-terminal glycine before transfer of Ubiquitin onto protein substrates. However, in most cases, E3s function as mere adaptors between E2s and substrates to confer reaction selectivity. Certain UbLs can be conjugated to themselves via the formation of isopeptide bonds between their C-terminal glycines and certain of their own lysines. This is especially true for ubiquitin, which can form chains involving each one of its seven lysines (K6, K11, K27, K29, K33, K48, K63). These chains can be homotypic or heterotypic due to the multiplicity of conjugatable lysines on Ubiquitin [7]. Mixed chains between different UbLs can also be formed. The best-known ones are those between Ubiquitin and SUMO or Nedd8 [8]. Importantly, UbL conjugation is reversible and highly dynamic with

most substrates being constantly modified and demodified. Deconjugation is carried out by isopeptidases, which cleave the isopeptide bonds between UbLs and target lysines. This allows UbLs, which are highly stable polypeptides, to be recycled and re-conjugated to other proteins. Some isopeptidases are also involved in the proteolytic maturation of UbLs, which are synthesized in the form of precursors displaying extra amino-acids at their C-termini. Similar to E3s, isopeptidases show substrate specificity or, at least, preference for particular chain linkages [9]. Concerning the SUMO pathway, deSUMOylases, such as SENP6 and SENP7, preferentially cleave SUMO-2 chains, whilst others, such as SENP-1 and SENP-2, rather deconjugate SUMO bound to target proteins [10]. Some deSUMOylases such as SENP-3, SENP-5 and USPL1 have preference for SUMO-2 over SUMO-1 [11, 12].

The consequences of UbL conjugation are numerous. They depend on the UbL type, possibly the nature of UbL chains formed and, obviously, the substrate. As they have been reviewed extensively elsewhere [3, 13–15], only the main physiological roles of Ubiquitylation, SUMOylation and Neddylation are considered hereafter.

The biological outcomes of Ubiquitin conjugation are highly dependent on the chain linkage types, which, due to their diversity and complexity, create the so-called “Ubiquitin code” [14]. The most abundant and best-characterized Ubiquitin chains are long K48-linked ones (>4 Ubiquitins). They constitute a protein degradation signal recognized by the 26S proteasome, which is the main cell proteolytic machinery [16–18]). This discovery led Avram Hershko, Irwin Rose and Aaron Ciechanover to be awarded the Nobel Prize in 2004. It is, however, important to keep in mind that K48-linked Ubiquitin chains can also be involved in signaling events and transcription regulation not involving protein destruction [19–21]. K63-linked chains are best-known as involved in protein-protein interactions, signaling, inflammatory response, DNA repair and ribosomal function [8, 22, 23]. K11 chains were shown to play important roles in cell cycle regulation and the activation of the NK- κ B pathway [24, 25]. Moreover, Ubiquitin can also form linear head-to-tail chains when its C-terminal glycine is linked to the N-terminal methionine of another Ubiquitin [26, 27]. Such chains are formed by the LUBAC complex and play key roles in immune signaling [28]. Finally, Ubiquitin can also be conjugated to protein substrates as monomers, sometimes at multiple sites, to regulate transcription, DNA repair or membrane receptor internalization and possibly degradation [29–31].

More than 6,000 SUMOylated proteins have been identified recently thanks to proteome-wide mass spectrometry approaches [32, 33]. SUMOylation modifies the surface of target proteins and,

thereby, alter their function and fate. In particular, SUMO can recruit SUMO-interacting motifs (SIM)-bearing proteins. However, only a handful of such effectors of SUMOylation have been identified so far. This is, for example, the case of the SUMO-targeted Ubiquitin ligases (StUBLs). These proteins, which include RNF4 [34, 35] and Arkadia/RNF111 [36] harbor multiple SIMs recognizing poly-SUMO-2 chains irrespectively of the substrate they are bound to. As the interaction between SUMO and SIMs is of low affinity, SUMOylation most often stabilizes an already existing interaction rather than promotes a new one. This is typically illustrated by the binding of the DNA helicase Srs2 to SUMO-modified PCNA [37]. Albeit SUMO has been involved in many cellular processes, its best-described functions are nuclear, consistently with a higher accumulation of SUMOylated proteins in the nucleus. In particular, SUMOylation plays key roles in DNA damage repair through the modification of critical proteins involved in this process [38]. SUMO also modifies a high number of proteins involved in gene expression (transcription factors, co-regulators, histones, transcription machinery) and participates in the regulation of transcription [39–43]. SUMOylation often concerns protein complexes comprising multiple SUMOylatable subunits. In this case, the biological outcomes are usually thought to result from SUMOylation of the complex irrespectively of the SUMOylation site or of the SUMOylated proteins within the complexes [44]. SUMOylation is highly regulated by stresses [45]. Some stresses affect limited number of SUMO substrates, while others can alter the activity of the whole pathway by affecting SUMO-conjugating- and/or -deconjugating enzymes. For example, upon proteotoxic stress induced by heat shock, SUMO-2 conjugation is quantitatively rewired to chromatin-bound proteins [46], which prevents protein aggregation and targets them for degradation by the Ubiquitin-proteasome system [47]. Oxidative stress is also a critical regulator of SUMOylation through its ability to induce the reversible inactivation of the SUMO E1 and E2 via the formation of a disulfide bond between their catalytic cysteines [48]. This redox regulation of SUMOylation participates in the activation of ATM kinase and is required for proper DNA damage response [49]. Reactive Oxygen species have also been involved in the regulation of specific SUMO E3 and isopeptidases [50].

Nedd8 (Neural precursor cell-expressed developmentally down-regulated 8) is the closest kin of Ubiquitin, as they share 60% of homology. Cullins, which are key components of the family of the multimeric cullin RING Ubiquitin ligases (CRL) are, by far, the most abundant Neddylated proteins. Cycles of Neddylated/deNeddylated are required for their Ubiquitin ligase activity [51]. Nedd8 is also conjugated to many non-cullin substrates [15]. These include transcription factors, such as p53 [52], TAp73 [53] and E2F1 [54, 55], as well as the VHL (Von-Hippel-

Lindau)[56], BCA3 (Breast-Cancer-Associated protein 3)[57], the chemokine receptor CXCR5 [58] and several ribosomal proteins [59–62]. In these cases, Neddylation is involved in their localization, stabilization or regulation of their interaction with partners [15]. Similarly to SUMOylation, Neddylation has also been implicated in the response to proteotoxic stresses [63].

Oncogenic and tumor suppressor pathways are controlled by UbLs

UbLs, through the variety of proteins they conjugate, are involved in each one of the "Hallmarks of cancer", as defined by Hanahan and Weinberg [64]. For reasons of space, it is impossible to summarize here all cancer-relevant pathways regulated by UbLs. The reader is, therefore, referred to recent comprehensive reviews on this subject [65, 66]. Below, we will focus only on pathways that are controlled by at least two UbLs.

The p53 pathway

The tumor suppressor protein p53 is certainly the best-studied transcription factor in cancer where its major cell protection functions are most often, if not always, lost. Physiologically, p53 participates in multiple cellular functions. They non-exhaustively include regulation of cell cycle and death, senescence, autophagy, DNA damage repair and metabolism. p53 is mutated in approximately 50% of tumors, where its mutations can be associated with oncogenic gains of function. In most of the other tumors, either the p53 gene is deleted or its activity, or that of its protein product, is inhibited following a diversity of mechanisms, which results in inability to control cell proliferation or to induce apoptosis or senescence [67].

The first and best-characterized p53 modification by UbLs is Ubiquitylation [68]. The main cellular E3 ligase for p53 is the MDM2 protein, which maintains low p53 levels under basal conditions via K48-linked chain Ubiquitylation and subsequent proteasomal degradation [69, 70]. Upon genotoxic stress, for example, this Ubiquitylation is arrested, permitting p53 to accumulate and to exert its cell protection functions. On the contrary, upon hyperactivity or amplification of the pro-oncogenic MDM2 gene, p53 is continuously maintained at a low level, favoring tumorigenesis [71]. A similar pro-oncogenic p53 inactivation process occurs in human papilloma virus (HPV) 16/18-infected cervix epithelial cells where the p53-interacting viral protein E6 recruits the cellular E6AP HECT E3 ligase [72, 73]. Interestingly, MDM2 can also mono-Ubiquitylate p53, which entails nuclear export and, thereby, inhibition of transcriptional activity [74]. Such a cytosolic export also impacts other p53 functions, including inhibition of autophagy and induction of apoptosis [75]. Other E3 Ubiquitin ligases such as MSL2 [76] and WWP1 [77]

were shown to target p53 to the cytosol without, however, affecting its proteasomal degradation. Finally, the E3 ligase E4F1 was reported to Ubiquitylate p53 on chromatin. E4F1 increases p53 ability to activate specific transcriptional programs related to cell cycle arrest without affecting its degradation [20](Figure 1)

p53 activity can also be controlled by Neddylation, which involves the E3 ligases activities of MDM2 [52], as well as that of FBOX11 [78]. Neddylation occurs on 3 lysines (370, 372, 373) and reduces p53 transcriptional activity [52, 78–80]. In addition, p53 Neddylation was shown to limit its Ubiquitin-mediated nuclear export [79].

Finally, p53 can also undergo modification by SUMO on its lysine 386 [81–83]. However, the role of this SUMOylation is still debated and might depend on the cellular context [84]. Indeed, p53 SUMOylation was initially described to increase its transcriptional activity [81, 82]. However, other studies showed that SUMOylation is involved in neither p53 localization nor transcriptional activity [85]. SUMOylation was also suggested to regulate p53 subcellular localization. For example, SUMOylation of mouse p53 was shown to be required for nuclear accumulation and enhanced stability in granulosa cells [86]. However, and contrasting with the latter observation, androgen-mediated SUMOylation of p53 was suggested to be important for export of p53 to the cytosol [87] (Figure 1).

The NF- κ B pathway

The NF- κ B pathway is overactive in a vast majority of cancers where it is thought to participate in cancer cell resistance to apoptosis and sustained proliferation. This is especially true in hematological malignancies, where the function of various components of this pathway can be altered, notably by oncogenic mutations or rearrangements/translocations [88].

Under basal physiological conditions, the NF- κ B transcription factor is maintained latent in the cytoplasm through physical interaction with its I κ B α inhibitor [89]. Ubiquitylation is involved in its activation at several steps. A typical example of NF- κ B pathway activation is as follows. In response to an appropriate extracellular stimulus, the RIPK1 (receptor-interacting serine/threonine protein kinase 1) kinase, is modified with non-proteolysis-inducing linear Ubiquitin chains by the LUBAC complex and K11- and K63-linked chains by the cIAP1 (cellular inhibitor of apoptosis protein-1) Ring domain-bearing Ubiquitin E3 factor. These Ubiquitylations serve as a platform for recruiting a downstream kinase effector complex (made up of TAK1, TAB2/3, IKK γ /NEMO), which activates another kinase complex (IKK complex

made up of IKK α and IKK β). Finally, the latter phosphorylates I κ B α , which triggers its subsequent K48-linked Ubiquitylation and is followed by proteasomal degradation. The NF- κ B transcription factor is, thereby, released and can then enter the nucleus to activate its target genes [24].

In the early days of the SUMO field, it was discovered that SUMOylation of I κ B α competes with Ubiquitylation by targeting the same lysine residue (Lys 21)[90]. SUMOylation is also involved in the regulation of NEMO activity. In particular, NEMO gets SUMOylated upon genotoxic stress. This leads to its addressing to the nucleus and subsequent ATM-dependent Ubiquitylation and activation of the IKK complex in the cytoplasm [91].

Finally, it has been suggested that NEMO is Neddylated, which inhibits the NF- κ B pathway [92]. Neddylation was also involved in the regulation of NF- κ B-dependent transcription through modification of BCA3, one of its partners in chromatin. BCA3 Neddylation recruits the deacetylase SIRT1 and, thereby, was proposed to repress transcription of NF- κ B target genes [57].

The TGF β pathway

The TGF- β (Transforming Growth Factor β) pathway generally exerts tumor suppressor activity in normal or premalignant cells but, on the contrary, often promotes tumorigenesis at later stages, including metastasis. Depending on the cell/tumor type, it can be involved in the regulation of cell proliferation, apoptosis, epithelial-mesenchymal transition (EMT) and cell migration [93].

In the canonical pathway, the binding of TGF- β to its cell membrane receptor (made up of two subunits, T β R-I and T β R-II) initiates a cascade of intracellular phosphorylation events. Among the first phosphorylated proteins are Smad-2 and Smad-3, which are transcription factors maintained latent in the cytoplasm in the absence of TGF- β receptor activation. Phosphorylated Smad-2 and -3 then assemble with the Smad-4 protein to form a trimeric complex that translocates into the nucleus where it binds to DNA and stimulates the expression of TGF- β target genes [94]. Interestingly, Ubls control this pathway at multiple and intermingled levels [95]. More specifically, Smad-7 is a cytoplasmic TGF- β -induced negative regulator of the pathway that can recruit Smurf-1 and Smurf-2 (Smad-specific E3 Ubiquitin ligase 1 and -2), two Ubiquitin ligases of the HECT family. These can Ubiquitylate T β R-I, leading to its degradation and, thereby, induce a negative feedback loop on the pathway [96, 97]. T β R-I Ubiquitylation, and consequently its degradation, can, however, be antagonized by the deUbiquitylase Usp15, which

associates with Smurf-2, and act as a positive regulator of the pathway [98]. Interestingly, Smurf-1 and -2 are positively regulated by Neddylation via particular mechanisms. Indeed, Nedd8 is, first, transferred from the Nedd8-conjugating E2 enzyme Ubc12 to the catalytic cysteine of Smurf-1 via the formation of a thioester bond. It is, then, transferred to lysines of Smurf-1. This Neddylation increases the recruitment of Ubiquitin E2(s) and, thereby, activates the Ubiquitylation of Smurf-1 protein substrates [99]. Noteworthy, Smurf-1 and -2 were also shown to bind non-covalently to Nedd8, which also contributes to increasing their Ubiquitin ligase activity [100].

Complexifying the picture, SUMO can also enter into the game at different levels, as diverse components of the TGF- β pathway can undergo SUMOylation with implications in cancer [101]. For example, SUMOylation of T β R-I increases the activation of Smad-3 with, as a biological consequence, enhancement of invasion and metastasis by Ras-transformed cells [102] and suppression of EMT in bladder cancer cells [103]. Smurf-2 is also SUMOylated (on lysines 26 and 369) thanks to the SUMO ligase PIAS3, which increases its Ubiquitin ligase activity and, hence, the degradation of T β R-I. In this case, important outcomes of T β R-I proteolysis consist of decreased TGF- β -induced cell proliferation and reduced invasion by breast cancer cells [104, 105]. Transcription factors downstream of the TGF- β pathway are also SUMOylated with sometimes antagonistic effects. For example, SnoN [106] and Sip1/Zeb2 [107] SUMOylations repress the pathway whereas those of Snail [108] and Slug [109] activate it. Finally, non-covalent SUMO binding might also be involved in the regulation of the TGF- β pathway. As a matter of fact, the already mentioned SUMO-targeted Ubiquitin ligase Arkadia/RNF111 can be recruited via its cluster of SIMs (i.e. most probably due to binding to SUMO-2 chains) to TGF- β pathway-target genes with, as a result, antagonization of the Polycomb repressor complex at the level of their regulatory domains [110].

PML-RARA in Acute Promyelocytic Leukemias

Acute Promyelocytic Leukemias (APL) are a minor subtype (< 10%) of Acute Myeloid Leukemias. In most cases, their main driver tumorigenic mutations consists of a t(15;17) chromosomal translocation engaging the PML and RARA genes, leading to the expression of an oncogenic fusion PML-RAR α . PML, which was initially viewed as a tumor suppressor, was one of the first SUMO substrates to be identified and is one of the most-abundantly SUMOylated proteins in the cell [111–113]. Through self-assembly, it forms the so-called membrane-less PML

nuclear bodies, which recruit many proteins thanks to SUMO-SIM interactions. Recruited proteins can undergo SUMOylation in PML bodies due to the presence of the SUMO E2 Ubc9 within these structures (Sahin *et al*, 2014). Physiologically, PML bodies are seen as structures fine-tuning a variety of cellular activities that include responses to stresses and viral infections, as well as control of cell death, senescence or DNA repair. It has long been known that they are disrupted by the PML-RAR α fusion protein in APL cells [115], which is essential for oncogenesis. Interestingly, the combination of arsenic trioxide and retinoic acid has been shown efficient at curing APL patients. Indeed, it consists of the first successful oncogenic protein-targeted therapy that has been described [116]. In brief, the drug combination entails the polySUMOylation of PML-RAR α , which is followed by the recruitment of the StUbl RNF4 and, hence, its Ubiquitylation and degradation by the proteasome [34, 35]. An important consequence of PML-RAR α destruction is not only induction of cancer cell differentiation into short-lived granulocytes but also abrogation of cancer cell self-renewal through the reformation of PML nuclear bodies and subsequent p53 pathway activation [117].

Deregulations of UbL pathways in cancer

Many UbL enzymes are dysregulated in cancers

Many enzymes and regulators of UbL-conjugating and -deconjugating pathways are dysregulated in various cancers (Table 2) and there is increasing evidence linking these dysregulations to tumorigenesis, cancer progression, metastasis or resistance to anticancer drugs. For reasons of space, it is not possible to describe all dysregulations that have been reported in the literature. Some illustrative examples are, however, summarized below.

Dysregulation of the Ubiquitin pathway enzyme in cancer.

The Ubiquitin pathway is far more complex than the SUMO and Nedd8 pathways, which increases the possibilities of dysregulations associated with cancer (Table 2). Two particularly illustrative examples of dysregulations of this pathway are presented below.

The first one concerns the BIRC1 to -8 (baculovirus IAP repeat-containing protein; IAP standing for inhibitors of apoptosis proteins) family of Ubiquitin E3 ligases. These enzymes play key roles in the activation of the NF- κ B pathway and the inhibition of apoptosis. Their overexpression appeared associated with increased resistance to therapies and adverse prognosis [118]. This is

particular clear for BIRC4 (also called XIAP for X-linked inhibitor of apoptosis protein), which is overexpressed as early as the first stages of breast and colon carcinogenesis. This leads to inhibition of autophagy through the degradation of the autophagy receptor p62 and enhances tumor cell proliferation [119]. BIRC4 is also overexpressed in B-cell lymphomas and associated with weaker response to mitotic spindle poison-based chemotherapies. This is due to its increased stability resulting from its deUbiquitylation by the isopeptidase USP9X that is also overexpressed in the same tumors [120].

The second example deals with E3 ligases from the SCF (Skp1-Cullin1-F-box protein) family, which are also often dysregulated in cancer [121]. This is best-exemplified by various F-box proteins, which are the SCF components responsible for the specificity of substrate recognition [122]. For example, FBXW7 is a well-characterized tumor suppressor thanks to its ability to recruit oncogenic proteins such as c-Myc, c-Jun, c-Myb, Aurora-A for SCF-mediated Ubiquitylation and subsequent proteasomal degradation [123]. Consistently, disabling mutations of FBXW7 are found in numerous cancers. This is, for example, the case in T-cell Acute Lymphocytic Leukemias (T-ALL), with up to 30% of patients presenting mutations in its gene [124] but also in colorectal adenocarcinoma, uterine endometrial carcinoma and bladder carcinoma. Skp2 is another F-Box protein dysregulated in many cancers [125]. Its substrates include the cell cycle inhibitor p27^{Kip1}. Its overexpression in many cancers is associated with a bad prognosis and is generally inversely correlated to p27^{Kip1} expression [126]. The third F-Box, which is often dysregulated in cancer, is β -TRCP (also called FBW1A). It is overexpressed in various cancers, including colorectal tumors where it exerts prooncogenic actions through activating the β -catenin and NF- κ B pathways [127].

Overactivation of the Nedd8 pathway in cancer is often associated with bad prognosis

Strikingly, most enzymes of the Nedd8 pathway are overactivated in lung adenocarcinoma and squamous-cell carcinoma [128]. Along the same line, high Nedd8 expression is an adverse factor in nasopharyngeal carcinoma [99]. Moreover, the Nedd8-activating E1 (formed of the Nae1 and Uba3 subunits) and -conjugating E2 (Ubc12) enzymes were found upregulated in >2/3 of a 322 patient cohort with intra-hepatic cholangiocarcinoma, which was associated with higher global protein Neddylaton and tumor progression [129]. Finally, the Jab1/CSN5 protein, which is responsible for deNeddylaton of the members of the CRL family of Ubiquitin E3 ligases (see above), was found overexpressed in numerous cancers (breast cancer, ovarian cancer, hepatocellular carcinoma, non-small cell lung cancer, nasopharyngeal carcinoma, etc...) and

associated with adverse prognosis [130].

Dysregulations of the SUMO pathway in cancer

Increasing evidence suggests that both SUMO conjugation- and deconjugation machineries are dysregulated in various cancers (Table 2). Yet, the contributions of these alterations to tumorigenesis have not often been established formally in most cases [65]. Interestingly, the level of Uba2, the catalytic subunit of the SUMO-activating E1 enzyme, is increased in colorectal cancer tissues, the highest Uba2 expression being associated with both the highest colorectal cancer stages and the poorest prognosis [131]. The SUMO-conjugating enzyme Ubc9 is also overexpressed in many cancers. This is the case of hepatocellular carcinomas, where its overexpression participates in the resistance to chemotherapies [132]. HyperSUMOylation has also been described in Myc oncogene-driven lymphomas. This results from a strong transcriptional activation of the expression of most enzymes of the SUMO pathway and is essential for tumorigenesis [133]. Using synthetic lethality screens, it was also shown that Myc-overexpressing breast cancer cells are highly dependent on a functional SUMO pathway for growth and survival [134], pointing to a novel therapeutic windows through targeting SUMOylation enzymes in this cancer type. Finally, deSUMOylases of the SENP family are either up- or down-regulated in cancers. SENP1 is, for example, overexpressed in prostate cancer, where it promotes tumor formation and metastasis [135] and downregulated in osteosarcomas, which is important for the maintenance of cancer stem cells [136].

Targeting UbLs: new perspectives in cancer treatment

Considering their critical roles and their widespread dysregulations in cancer, UbL pathways have emerged as promising therapeutic targets. Considerable efforts have consequently been made worldwide to develop strategies to inhibit their enzyme components [137]. We will focus here on the strategies used to target E1, E2 and E3 factors. For information on the targeting of deconjugating enzymes, the reader is referred to recent review [138, 139]

E1 inhibitors

- Ubiquitin E1 inhibitors

PYR-41 and PYZD-4409 were the first described inhibitors of an Ubiquitin-activating E1 enzyme. They are based on a pyrazolidine cycle and were identified during chemical library screenings [140, 141]. They bind to UBE1 and inhibit the formation of the thioester bond with Ubiquitin. Whether they inactivate UBA6, the second Ubiquitin E1, has however not been

determined yet. PYZD-4409 was shown to induce apoptosis of Acute Myeloid Leukemia cells, with minimal toxicity for normal hematopoietic cells. It also displayed anti-tumoral activity *in vivo* in mice xenografted with human AMLs [140]. A more potent inhibitor of UBE1, TAK-243 (also known as MLN7243), was generated recently by Takeda Pharmaceuticals [142]. It forms an adduct with Ubiquitin and inhibits UBE1 in the nanomolar range. When used on cell lines, it leads to cell cycle arrest, induction of ER stress and impaired DNA damage response. Interestingly, TAK-243 showed (i) anti-tumor activity *in vivo* in immunodeficient mice subcutaneously grafted with various human tumor cell lines [142] and (ii) anti-leukemic activity on primary human AML cells both *in vitro* and *in vivo* after xenografting to immunodeficient mice (PDX) [143]. Finally, in a phase I dose-escalation clinical trial (clinicaltrial.gov identifier: NCT02045095) involving 29 patients with advanced solid tumors, it however, entailed serious adverse events in more than 1/3 of the individuals treated. Its *in vivo* efficacy could be demonstrated by immuno-histochemistry using antibodies directed to either polyUbiquitin chains or Ubiquitylated-histone H2B (uH2B; which is the second most Ubiquitylated proteins in mammalian cells after Ubiquitylated H2A). A second phase I trial is scheduled to start soon with patients undergoing relapse or suffering from hematological malignancies refractory to standard chemotherapies (clinicaltrial.gov identifier: NCT03816319)

- Nedd8 E1 inhibitors

MLN4924, also called TAK-924 or pevonedistat for its clinical form, is the first mechanism-based inhibitor of a Ubl E1 enzyme that was designed by the Millenium-Takeda company. As TAK-243, MLN4924 is an ATP-competitive inhibitor of the Nedd8-activating E1 enzyme NAE. It forms a covalent adduct with Nedd8, which is catalyzed by NAE. The adduct cannot be transferred to Nedd8 E2s, blocking the activity of the E1, including *in vivo* [144]. Initial experiments showed that the treatment of immunocompromized mice xenografted with HCT-116 colon cancer cells with MLN4924 led to increased DNA-damage in cancer cells and limited tumor growth [145]. MLN4924 was then shown to have promising antitumoral activity in various preclinical cancer models, including patient-derived xenografts (PDX). Several phase I clinical trials in cancer patients have shown it is well tolerated [146–148] and various phase II trials have now been launched, in particular to treat hematological malignancies. MLN4924 was also shown to synergize, both *in vitro* and *in vivo*, with genotoxic drugs such as Cytarabine [149] or the demethylating agent Azacytidine [150] in AMLs. A phase Ib clinical trial in elderly patients unfit for conventional chemotherapies suggests a potential clinical benefit for the combination of Azacytidine and Pevonedistat [151]. A randomized phase III trial involving 450 patients with

AML, CML (Chronic Myelomonocytic Leukemia) or MDS (Myelodysplastic syndrome) is now ongoing to prove the efficacy of this combination on a large scale (clinicaltrial.gov identifier: NCT03268954)

- SUMO E1 inhibitors

Ginkgolic acid was identified as an inhibitor of the SUMO-activating E1 enzyme during a screening using botanical extracts. This molecule, and its anacardic acid derivative, were shown to bind to the E1 and to inhibit the transfer of SUMO from the E1 to the E2 [152]. Anacardic acid was shown to inhibit cell division, to induce apoptosis and/or to inhibit migration of various cancer cell lines and primary samples [153–157]. It was also shown to limit tumor growth in mice xenografted with human KG1a AML cells [153]. However, anacardic acid is not a potent SUMOylation inhibitors, as it requires concentrations above 25 μ M to inhibit SUMOylation when used on cultured cells [152] and its use in preclinical models is unfortunately limited by its very poor solubility. Moreover, anacardic acid has been shown to inhibit various other enzymes, the best characterized one being the Histone Acetyl Transferase p300 [158]. Recently, Takeda Pharmaceutical has developed ML-792, a mechanism-based inhibitor of the SUMO E1 with nanomolar potency [159]. Similarly to the other UbL E1 inhibitors developed by Takeda Pharmaceutical, it forms a covalent adduct with SUMO that is catalyzed by the SUMO E1. Treatment of cell lines with this inhibitor induces strong mitotic defects, which leads to their apoptosis. Interestingly, ML-792 preferentially affects the proliferation and viability of cancer cells overexpressing the Myc oncogene *in vitro* [159].

E2 inhibitors

Few inhibitors inhibiting UbL-conjugating E2 enzymes have been discovered so far and none of them is used in clinical trials yet.

The NSC697923 molecule was originally identified in a screen for molecules inhibiting the NF- κ B pathway. It actually binds to the catalytic cysteine of the Ubc13-Uev1A Ubiquitin E2 that catalyzes the formation of K63-linked polyUbiquitin chains. Thereby, it prevents the formation of the thioester bond with Ubiquitin [160, 161]. This inhibitor limits the proliferation of diffuse large B-cell lymphoma cells *in vitro* [160]. BAY 11-7082, which was also initially reported as an inhibitor of the NF- κ B pathway, was subsequently shown to inhibit K63-linked polyUbiquitin chains formation by targeting the catalytic cysteines of Ubc13 and UbcH7 [162]. CC0651 is an allosteric inhibitor of the CDC34 Ubiquitin E2, which is associated with Ubiquitylation by cullin-RING ligases. It prevents the discharge of Ubiquitin to acceptor lysines on the target proteins. In

particular, this molecule leads to an accumulation of the CDK inhibitor p27^{kip1}, a target of the SCF complex, which contributes to decreased cancer cell lines proliferation [163, 164]. Using a virtual screening, the triazine analog SMI#9 was identified as an inhibitor of the Ubiquitin E2 Rad6B via binding to its catalytic site [165]. This molecule was shown to enhance cancer cell sensitivity to platinum-based drugs, including *in vivo* [166].

Small molecules targeting the SUMO E2 Ubc9 have also been identified in various screens. Spectomycin B1, which was originally identified as an antibiotic, directly binds to Ubc9 and prevents to formation of the Ubc9-SUMO thioester bond. It inhibits ER α -regulated gene expression and growth of ER α -positive breast-cancer cell lines [167, 168]. The flavonoid derivative 2-D08 was found to inhibit the transfer of SUMO from Ubc9 to target proteins [169]. Moreover, 2-D08 also sensitized non-promyelocytic AML cells to retinoids-induced differentiation and death both *in vitro* and *in vivo* [170]. Unfortunately, all of these SUMO E2 inhibitors have low potency and poor solubility, which prevents their use in therapy.

E3 inhibitors

Inhibiting E1 or E2 enzymes affects the activity of the whole UbL pathway, which may entail deleterious effects on normal, non-cancerous cells. Targeting E3s is consequently considered as a more specific and, potentially, less toxic approach in living individuals. To date, no molecule targeting SUMO or Nedd8 E3s has been identified. By contrast, many molecules targeting Ubiquitin E3s have been discovered [171], as illustrated below in the case of MDM2 and IAPs.

- MDM2 inhibitors

As mentioned previously, MDM2 is physiologically responsible for the Ubiquitylation of the tumor suppressor p53, but is overexpressed in numerous cancers, preventing p53 pathway activation, in particular in case of genotoxic insults. Inhibiting MDM2 pharmacologically therefore constitutes an intense research area with several molecules in preclinical development and others already in clinical trials [172]. Nutlins are imidazoline compounds, which compete with p53 for the binding to MDM2. Such a competition restores the p53 pathway via inhibiting p53 degradation and induces cell cycle arrest and apoptosis of cancer cell lines both *in vitro* and *in vivo* [173]. RG7112, a member of the Nutlin family, was the first MDM2 inhibitor to be used in phase I clinical trials, in particular for liposarcoma- [174] and hematological malignancies-presenting patients [175]. This compound was shown to efficiently activate p53 in these tumors and a fraction of patients showed a clinical response. However, therapy-related adverse events

were observed in most of treated individuals. Quite similarly to Nutlins, MI-219 mimicks p53 primary structure motifs, binds to MDM2 and prevents its association with p53. It permits robust inhibition of tumor growth *in vivo* without affecting normal tissues in mouse cancer models [176]. AMG-232 is also to be added to the list of small molecules inhibiting the p53-MDM2 interaction [177]. This molecule, which can be administered orally and is highly potent, is currently tested in phase I and II clinical trials [178]. Another emerging approach to target the p53/MDM2 interaction is the use of stapled peptides. These peptides mimick α -helixes through side-chain crosslinking between non-natural amino acids introduced in the peptide during synthesis [179]. ALRN-6924 is a stapled peptide that efficiently disrupts the p53/MDM2 interaction, activates p53-dependent transcriptional programs and shows a robust antileukemic activity in mouse preclinical models [180]. Phase I/II trials are ongoing in patients with solid tumors and hematological malignancies (clinicaltrial.gov identifier: NCT02264613, NCT02909972).

- IAP inhibitors

As presented above, IAP/BIRC family members are Ubiquitin E3 ligases, which inhibit apoptosis by preventing, directly or indirectly, the activation of Caspase-3 and -9. SMAC is a mitochondrial antagonist of IAPs binding to their BIR domain and, thereby, preventing their activation. SMAC-mimetics mimicking the N-terminal residues of SMAC induce the dimerization of IAPs, which is followed by auto-Ubiquitylation and subsequent degradation [181]. These molecules were shown to have anti-tumoral activity as single agents or when combined with cytotoxic agents in various preclinical models. For example, Birinapan is a bivalent SMAC mimetic that was shown to activate RIPK-1-dependent apoptosis in relapsed and refractory Acute Lymphoblastic Leukemias (ALL) and to efficiently limit tumor growth *in vivo* [182]. It was also shown to synergize with various drugs, including the DNA-demethylating agent 5-azacytidine in AMLs [183]. A phase I clinical trial showed that it is well tolerated and leads to an important reduction of cIAP1 and the activation of cell-death pathways in the tumors and PBMCs (peripheral blood mononuclear cells) from the treated patients [184]. Similar results were obtained with LCL161, another SMAC mimetic under clinical development [185].

Conclusion

In conclusion, SUMO, Nedd8 and Ubiquitin play key roles in the control of essential cellular pathways and functions that are often dysregulated in cancer and/or participate to cancer response to therapies. Moreover, enzymes of SUMO, Nedd8 and Ubiquitin pathways are also dysregulated

in many tumor types. They therefore constitute attractive therapeutic targets. Intense efforts by academic and industry laboratories have recently been made to discover small pharmacological agents targeting them. A number of these are now being tested in early phase clinical trials and others are about to enter clinical testing. This might pave the way to better cancer treatment.

Acknowledgements

We are grateful to all members of the "Oncogenesis and Immunotherapy" group of IGMM for support and fruitful discussions. Funding was provided by the CNRS, Ligue Nationale contre le Cancer (Programme Equipe Labellisée), INCA (ROSAML), Association Laurette Fugain (contract ALF-2017/02), the Fondation ARC (to PG), the Fédération Leucémie Espoir, The EpiGenMed Labex and the ANR under the "Investissements d'avenir" programme (ANR-16-IDEX-0006).

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| Modifier | Homology with ubiquitin | E1 | E2 | E3 | Protease | Functions |
|-----------|-------------------------|------------|--------------|---------------------|----------------------------|----------------------------------------------------------|
| Ubiquitin | 100 | UBE1, UBA6 | 38 | >600 | ~100 | Multiples, proteasomal degradation |
| SUMO1-5 | 15 | SAE1/SAE2 | UBC9 | >15 | ~10 | Protein/protein interaction, regulation of transcription |
| NEDD8 | 58 | NAE1/UBA3 | UBC12, UBE2F | >10 | CSN5, NEDP1 | Cullins activation, cell cycle |
| ISG15 | 27 | UBE1L | UBCH8 | HERC5, EFP, HHARI | USP18 | Immune response, response to stress |
| FUB1 | 36 | | | | | Unknown, immune response regulation |
| FAT10 | 27 | UBA6 | USE2 | | 0 | Proteasomal degradation |
| URM1 | 17 | UBA4 | | | | tRNA thiolation, oxydative stress response |
| UBL5 | 25 | | | | | RNA splicing, cell polarisation |
| UFM1 | 23 | UBA5 | UFC1 | UFL1 | UFSP1, UFSP2 | Hematopoiesis, NF-κB regulation |
| ATG8 | | ATG7 | ATG3 | | ATG4 | Autophagy |
| ATG12 | 12 | ATG7 | ATG10 | | 0 | Autophagy |
| MAP1LC3A | 9 | ATG7 | ATG3 | ATG12, ATG5, ATG16L | ATG4A, ATG4B, ATG4C, ATG4D | Autophagosomes formation |
| MAP1LC3B | 13 | | | | | |
| MAP1LC3C | 10 | | | | | |
| GABARAP | 8 | | | | | |
| GABARAPL1 | 12 | | | | | |
| GABARAPL2 | 14 | | | | | |
| GABARAPL3 | | | | | | |

Table 1: Ubiquitin-like modifiers: conjugation/deconjugation enzymes and main functions

| UbL | Enzyme | Enzyme | Dysregulation | Cancer | Reference |
|-------|--------|----------------|-------------------------|---------------------------------------------------|------------|
| Ub | DUB | OTUB1 | Overexpression | lung, breast, ovarian, glioma, colon, gastric | [186] |
| | | UCHL1 | Underexpression | pancreatic | [187] |
| | | USP10 | Underexpression | small intestinal adenocarcinoma | [188] |
| | | USP10 | Underexpression | lung | [189] |
| | | USP18 | Overexpression | breast | [190] |
| | | USP22 | Overexpression | Colorectal, breast | [191, 192] |
| | | USP3 | Overexpression | gastric | [193] |
| | | USP32 | Overexpression | SCL | [194] |
| | | USP33 | Underexpression | gastric | [195] |
| | | USP34 | Overexpression | Diffuse large B-cell lymphoma | [196] |
| | | USP37 | Overexpression | Breast | [197] |
| | | USP39 | Overexpression | Renal, colorectal, lung | [198-200] |
| | | USP4 | Overexpression | melanoma | [201] |
| | | USP49 | Underexpression | pancreatic | [202] |
| | | USP5 | Overexpression | Pancreatic | [203] |
| | | USP7 | Overexpression | Osteosarcoma, medulloblastoma | [204, 205] |
| | | USP8 | Overexpression | cervical | [206] |
| | | USP9X | Overexpression | Pancreatic, breast | [207, 208] |
| | E2 | UBE2D1 | Overexpression | Hepatocellular carcinoma | [209] |
| | | UBE2L3 | Overexpression | NSCL | [210] |
| | | UBE2S | Overexpression | Hepatocellular | [211] |
| | | UBE2T | Overexpression | Hepatocellular, gastric | [212, 213] |
| | E2/E3 | UBE2O | Overexpression/mutation | Gastric, lung, breast, prostate, colorectal, TNBC | [214, 215] |
| | E3 | ciAP2 | Overexpression | Gallbladder | [216] |
| | | COP1 | Overexpression | Breast, ovarian, leukemia, melanoma, lung | [217, 218] |
| | | CUL-1 | Overexpression | colorectal | [219] |
| | | CUL-2 | Overexpression | colorectal | [219] |
| CUL-3 | | Overexpression | nasopharyngeal | [220] | |

| | | | | | |
|--|--|--------|-----------------|---------------------------------------------------------------------------------------------|-----------|
| | | E6AP | Overexpression | Prostate, NSCL | [221–223] |
| | | FBX011 | Overexpression | gastric | [224] |
| | | FBX016 | Underexpression | Glioblastoma | [225] |
| | | FBX017 | Overexpression | lung | [226] |
| | | FBX031 | Underexpression | gastric | [227] |
| | | FBX032 | Underexpression | breast | [228] |
| | | FBXW7 | Underexpression | Acute lymphoblastic leukemia, colorectal, esophageal, gastric, hepatocellular, NSCL, breast | [229] |
| | | HUWE1 | Overexpression | Breast, lung, prostate, larynx, stomach, uterus | [230] |
| | | | Underexpression | brain | |
| | | ITCH | Overexpression | Lung, CLL, breast | [231–234] |
| | | LZTR1 | Mutation | RAS-driven cancers | [235] |
| | | MDM2 | Overexpression | Retinoblastoma, glioblastoma, colorectal, melanoma, breast | [236–238] |
| | | NEDD4 | Overexpression | Lung, bladder, pancreatic, colorectal | [239–242] |
| | | NEDD4L | Underexpression | Colorectal, pancreatic, melanoma, lung, ovarian, prostate | [243–247] |
| | | Pirh2 | Overexpression | Glioma, head and neck, prostate, lung, hepatocellular | [248–252] |
| | | RNF138 | Overexpression | glioma | [253] |
| | | RNF146 | Overexpression | colorectal | [254] |
| | | RNF185 | Overexpression | gastric | [255] |
| | | RNF20 | Underexpression | breast, lung, prostate cancer, clear cell renal cell carcinoma, mixed lineage | [256] |

| | | | | | |
|------|-----|--------|-----------------|-----------------------------------------------------------------------|------------|
| | | | | leukemia | |
| | | RNF43 | Underexpression | gastric | [257] |
| | | RNF7 | Overexpression | prostate | [258] |
| | | SIAH1 | Underexpression | Hepatocellular carcinoma, gastric | [259, 260] |
| | | SIAH2 | Overexpression | Breast, lung, pancreatic, prostate, liver, melanoma | [259] |
| | | SKP2 | Overexpression | Hepatocellular, lung, oral squamous cell, glioblastoma | [261–264] |
| | | SMURF1 | Overexpression | Ovarian, thyroid, gastric, glioma, pancreatic | [265–269] |
| | | SMURF2 | Overexpression | Renal, breast, esophageal | [270–272] |
| | | TRIM11 | Overexpression | Prostate, hepatocellular | [273–275] |
| | | TRIM25 | Overexpression | Prostate, NSCL, colorectal | [276–278] |
| | | | Underexpression | hepatocellular | [279] |
| | | TRIM28 | Overexpression | Prostate | [280] |
| | | TRIM31 | Overexpression | Gallbladder, hepatocellular | [281, 282] |
| | | TRIM45 | Underexpression | glioblastoma | [283] |
| | | TRIM56 | Underexpression | Multiple myeloma, ovarian | [284, 285] |
| | | UBR5 | Overexpression | TNBC | [286] |
| | | WWP1 | Overexpression | AML, prostate, breast, gastric, osteosarcoma | [287–291] |
| | | WWP2 | Overexpression | Glioma, lung adenocarcinoma | [292, 293] |
| | | XIAP | Overexpression | Breast, colon | [119] |
| SUMO | DUB | SENP1 | Overexpression | NSCL, colorectal, renal, hepatocellular, prostate, breast, astrogloma | [294–302] |
| | | | Underexpression | osteosarcoma | [303, 304] |
| | | SENP2 | Underexpression | Bladder, gastric, | [305–307] |

| | | | | | |
|-------|-----|----------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------|
| | | | | chronic lymphocytic leukemia | |
| | | SENP3 | Overexpression | ovarian | [308] |
| | | SENP5 | Overexpression | hepatocellular | [309] |
| | E1 | SAE1/2 | Overexpression | Gastric, colorectal, breast, prostate, pancreatic, hepatocellular | [131, 310, 311] |
| | E2 | UBC9 | Overexpression | Breast, prostate, pancreatic, osteosarcoma, hepatocellular | [310, 312, 313] |
| | E3 | PIAS1 | Underexpression | breast | [314] |
| | | | Overexpression | Prostate, multiple myeloma | [315–317] |
| PIAS3 | | Overexpression | colorectal | [310] | |
| NEDD8 | DUB | Jab1/CSN5 | Overexpression | Breast, ovarian, hepatocellular, NSCLC, Oral squamous cell, Laryngeal, thyroid, pancreatic, esophageal, colorectal, gastric | [318] |
| | E3 | C-CBL | Underexpression | lung | [319] |

Table 2: Dysregulation of UbL enzymes in cancer. This table summarizes the known dysregulations of these enzymes. It comprises the main enzymes in each pathway but is not necessarily exhaustive.

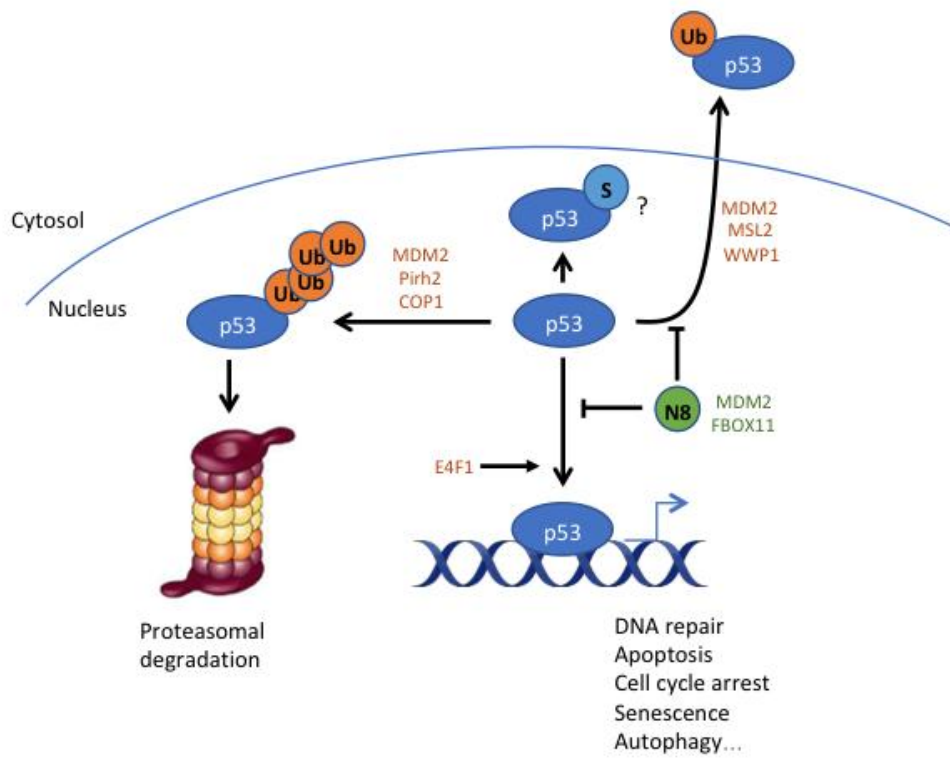


Figure 1: Regulation of p53 by UbL. N8: Nedd8, Ub: Ubiquitin, S: SUMO