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Review

Role of APD-Ribosylation in Bone Health and Disease

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Abstract: The transfer of adenosine diphosphate (ADP)-ribose unit(s) from nicotinamide adenine dinucleotide (NAD^+) to acceptor proteins is known as ADP-ribosylation. This post-translational modification (PTM) unavoidably alters protein functions and signaling networks, thereby impacting cell behaviors and tissue outcomes. As a ubiquitous mechanism, ADP-ribosylation affects multiple tissues, including bones, as abnormal ADP-ribosylation compromises bone development and remodeling. In this review, we describe the effects of ADP-ribosylation in bone development and maintenance, and highlight the underlying mechanisms.

Keywords: ARTDs; ADP-ribosylation; bone; osteoclasts; osteoblasts; adipocytes

1. Introduction

Adenosine diphosphate (ADP)-ribosylation is the transfer of ADP-ribose units from nicotinamide adenine dinucleotide (NAD^+) to acceptor proteins [1,2]. This post-translational modification (PTM) either occurs as mono-ADP-ribosylation (MARylation) or poly-ADP-ribosylation (PARylation) upon attachment of a single or up to 200 ADP-riboses to targeted proteins, respectively [1–6]. ADP-ribosylation is catalyzed by ADP-ribosyltransferases (ARTs), which include diphtheria toxin-like ARTs (ARTDs), also known as poly(ADP-ribose) polymerases (PARPs), and cholera toxin-like ARTs (ARTCs), and some sirtuins (SIRTs) [1,2]. The human genome encodes 17 ARTDs, 4 ARTCs, and 7 SIRT members [1,2,7]. While PARylation, which can be linear or branched, is carried out by ART family members such as ARTD1, ARTD2, ARTD5, and ARTD6, MARylation is the function of a subset of ARTDs (e.g., ARTD3, ARDT10, and ARTD14), ARTCs (ARTC1 and ARTC5), and SIRTs (SIRT4 and SIRT6) [1,2,7,8]. ADP-ribosylation is reversible, as ADP-riboses are removed from MARylated proteins by enzymes such as ADP-ribosyl hydrolases (ARH1 and ARH3), terminal ADP-ribose protein glycohydrolase 1 (TARG1), macrodomains (MacroD1 and MacroD2), and from PARylated proteins by ARH3 and poly(ADP-ribose) glycohydrolase (PARG) [2,8,9]. By modifying or regulating proteins endowed with structural roles (e.g., histones), signaling functions, (e.g., mitogen-activated protein kinases, MAPKs), or transcriptional activities (e.g., transcription factors) [10–14], ARTs profoundly influence the whole organism homeostasis through regulation of countless cellular events, including transcription, replication, proliferation, differentiation, and survival [13,15–17]. Structural homologies, activity specificities, and cellular distributions of ARTs, as well as non-skeletal pathologies caused by these proteins, have been comprehensively reviewed elsewhere [1,2,4,16,18,19], therefore, this review does not discuss these topics, but focuses on bone regulation by ADP-ribosylation.

During development, mesenchymal condensations ossify directly or indirectly via a cartilaginous template, embryonic events known as intramembranous and endochondral ossification, respectively, where bone formation by the osteoblasts dominates bone resorption by the osteoclasts [20–22]. Postnatally, particularly during adulthood, bone resorption is offset by bone formation, a coupling

process that preserves bone mass and biomechanical properties (Figure 1). An imbalance between bone resorption and formation underlies a variety of diseases featured by excessive bone gain or loss [23–25]. While the osteoclasts arise from hematopoietic stem cells, the osteoblasts derive from mesenchymal stem cells (MSCs), which can also differentiate into adipocytes and chondrocytes under the influence of specific environmental cues [26,27], as detailed below. Excessive bone marrow adipogenesis at the expenses of osteogenesis has deleterious effects on bone, a tissue in which various cell types, including mesenchymal and hematopoietic cells, express a repertoire of ARTs and SIRTs. We review the impact of ADP-ribosylation on the differentiation of the osteoclasts, osteoblasts, and adipocytes, focusing on ART and SIRT members with a functional link to bone health and disease.

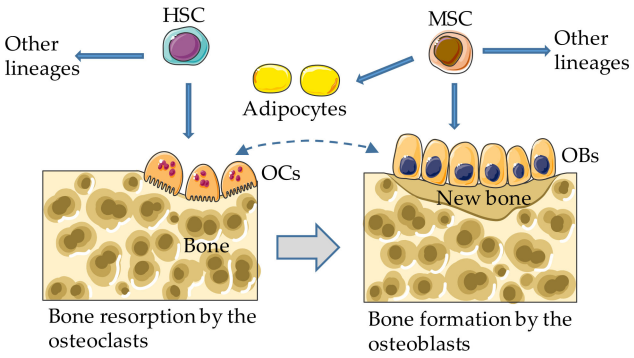

Figure 1. Bone remodeling. In adults, the osteoclasts (OCs) and other hematopoietic lineages (not depicted) arise from bone marrow hematopoietic stem cells (HSCs); the osteoblasts differentiate from mesenchymal stem cells (MSCs), which can also develop into adipocytes and other lineages (not depicted). Dashed and gray arrows indicate bidirectional regulatory interactions and coupling between bone resorption and formation, respectively.

2. Osteoclast Differentiation

During development, the emerging ossification centers recruit myeloid progenitors where they undergo terminal differentiation into the osteoclasts, which resorb the mineralized matrix, an action that over time results in the formation of the bone marrow cavity [28–30]. Postnatally, the damaged or old bone matrix is sensed and removed by the osteoclasts, and is evenly replaced by the osteoblasts. Potential sensors of defective bone matrix components include the innate immune complex, NOD-like receptor family (NLR), pyrin domain containing 3 (NLRP3) inflammasome, which is activated by bone matrix degradation products and promotes osteoclast differentiation [31, 32]. While bone marrow myeloid precursors (e.g., $CD11b^{low}CD115^{high}CD117^{high}$-expressing cells) differentiate into the osteoclasts in homeostatic conditions, circulating monocytes are capable of forming osteoclasts or fusing with pre-existing multinucleated osteoclasts in pathological settings, such as inflammatory arthritis [33–38]. Osteoclast differentiation, activity, and survival depend on macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL), whose expression and signaling outputs are regulated by various factors such as hormones (e.g., parathyroid hormone, estrogen, and 1,25α-dihydroxyvitamin D3) and pro-inflammatory cytokines, including those of the tumor necrosis factor (TNF) and interleukin-1 (IL-1) families [23–25,39]. For simplicity, this review focuses on osteoclast differentiation, though other biological aspects of these cells, such as activity and survival, are occasionally described. M-CSF, RANKL, and the majority of osteoclast-regulating factors are mainly produced by cells of the osteoblast lineage, and immune cells (e.g., macrophages, T and B lymphocytes) though the osteoclasts themselves produce factors such as sphingosine-1-phosphate and Wnts, which act not only in autocrine manner, but also paracrine fashion, regulating the functions of neighboring cells such as the osteoblasts [40–45]. Osteoclast differentiation is driven by complex interactions among various transcription factors, including the nuclear factor of activated T cells cytoplasmic 1 (NFATc1), NF-κB, and c-Fos [46]. While the effects of PTMs such as phosphorylation, methylation, ubiquitination, and SUMOylation on transcriptional regulation and

other key osteoclastogenic events have been extensively studied [47–55], only a few studies have investigated the role of ADP-ribosylation in osteoclast biology.

2.1. Role of ARTD1 in Osteoclast Differentiation

ARTD1 is the most studied member of the ARTD family in the skeleton. Early studies show that ARTD1 protein levels decline during in vitro osteoclast differentiation induced by RANKL, a response that correlates with increased expression of the a3 isoform of the V-ATPase subunit, tartrate-resistant acid phosphatase, and brain-type creatine kinase [56–59]. In agreement with the proposition that ARTD1 is a negative regulator of osteoclastogenesis, this protein binds to and represses the activity of the promoters of the aforementioned genes in the osteoclast precursors [56–59]. Follow up studies using engineered mice expressing uncleavable ARTD1 or *Artd1*-deficient mice, not only reinforce the anti-osteoclastogenic functions of ARTD1, but also shed light into the underlying mechanisms [60–63]. Novel insights include the demonstration that i) ARTD1 inhibits histone3lysine4 trimethylation (H3K4me3), histone marks of active chromatin, at the promoters of key osteoclastogenic factors such as B lymphocyte-induced maturation protein 1 (Blimp1), and ii) ARTD1 PARylates itself during osteoclast formation, a prerequisite modification that targets this protein for destruction through the proteasome pathway [63]. ARTD1 also inhibits H3K4me3 and H4 acetylation, thereby impeding the recruitment of the RelA subunit of NF-κB to the IL-1β promoter [61]. Progressive decline in ARTD1 levels also occurs during the differentiation of myotubes, which are multinucleated fibers that arise from the fusion of myoblasts [64]. The basis for the apparent inverse correlation between ARTD1 abundance and multinucleation is unclear, though it is tempting to speculate that the degradation of this enzyme, whose activity can deplete total intracellular NAD^+ levels by 80% may be necessary to prevent energy collapse during the high energy-demanding differentiation process.

Mice lacking ARTD1 globally or selectively in myeloid cells indistinguishably exhibit a low bone mass phenotype associated with an increased number of the osteoclasts on bone surfaces (Wang et al., personal communication). Consistent with the view of osteoclast lineage autonomous actions of ARTD1, in vitro osteoclastogenesis from isolated mouse bone marrow cells is higher in *Artd1* null cells compared to wild-type controls [61]. Potential ARTD1 substrates include the master regulators of osteoclast differentiation, NF-κB and NFATc1, which are PARylated by this enzyme in T cells and smooth muscle cells [65–69]. However, such interplay is unlikely in light of the recent study indicating that PARylated NF-κB and NFATc1 are undetectable in cells of the osteoclast lineage. Instead, ARTD1 consistently PARylates histone H2B among other proteins, and decreases the occupancy of H2B at the NFATc1 promoter, thereby inhibiting NFATc1 expression and restraining osteoclast differentiation (Wang et al., personal communication).

ARTD1 is cleaved at D214 into 89 kDa and 24 kDa fragments, presumably by caspase-7, in response to activation of the NLRP3 and NLR, CARD containing 4 (NLRC4) inflammasomes [63,70–72]. Consistent with its pro-inflammatory actions, loss of ARTD1 partially protects joints from destruction in the mouse model of collagen antibody-induced arthritis [73–77]. In line with the ability of ARTD1 and its cleaved fragments to activate signaling platforms such as the NF-κB pathway, knockin mice expressing uncleavable ARTD1 are resistant to ischemia/reperfusion-induced inflammation in intestine and kidney [60,65]. Unexpectedly, this ARTD1 mutant does not affect inflammatory outcomes induced by hyperactive NLRP3 inflammasome [62]. These conflicting results may be explained by the fact that ARTD1 actions are cell-context-dependent. Indeed, ARTD1 promotes NF-κB PARylation or activity in cultured smooth muscle cells, neuronal cells, and macrophages, while negatively regulating this transcription factor in lymphocytic leukemia cells [65,66,68,72]. Despite some gaps in our understanding of ARTD1 mechanisms of action, evidence overwhelmingly indicates that this enzyme negatively regulates osteoclast development (Figure 2).

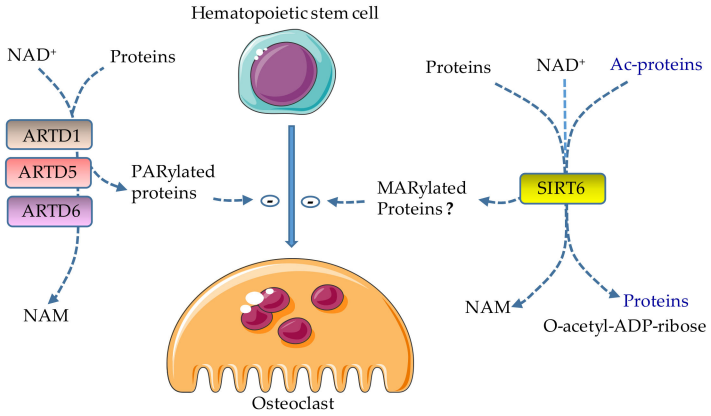

Figure 2. Effects of ADP-ribosylation on osteoclast formation. ARTD1, ARTD5, and ARTD6 catalyze the attachment of ADP-ribose polymers from NAD^+ to target proteins (PARylation), releasing nicotinamide (NAM) in the process; their actions lead to the inhibition of osteoclast differentiation. SIRT6 inhibits osteoclast development; however, the effects of its MARylating actions in this process are not clear because this enzyme also has deacetylase activity. Lysine deacetylation is coupled to NAD^+ hydrolysis, yielding a deacetylated targeted protein, O-acetyl-ADP-ribose, and NAM. Ac, acetyl.

2.2. Role of ARTD5 and ARTD6 in Osteoclast Differentiation

ARTD5 (also known as PARP5A or tankyrase 1) and ARTD6 (also referred to as PARP5B or tankyrase 2) [8] are expressed by many cell types, including the osteoclast lineage [78–81]. ARTD5 and ARTD6 are implicated in a range of biological processes, including DNA repair, glucose homeostasis and energy expenditure, and skeletal metabolism (through their interactions with the adaptor protein SH3 domain-binding protein 2, SH3BP2 and AXIN 1/2) [78,82–86]. PARylation targets SH3BP2 for ubiquitination by the E3-ubiquitin ligase RNF46, and subsequently for degradation [78,87]. Missense mutations in *SH3BP2* result in SH3BP2 that is stable, as it escapes the destructive actions of ARTD5 and ARTD6, and are associated with cherubism, a hereditary childhood-onset autoinflammatory disorder, whose severity regresses after puberty [88]. Focal facial bone lesions and deformities associated with the destruction of the jaws and dental complications characterize this disease [88]. Knockin mice expressing the most common disease-associated allele develop systemic inflammation (e.g., excessive TNF-α production) and bone loss due to massive osteoclast differentiation as a consequence of heightened sensitivity to M-CSF- and RANKL-induced signals; these events ultimately cumulate in hyperactivation of osteoclastogenic pathways such as Src, Syk, ERK1/2, and NFATc1 [78,79]. Conversely, *Sh3bp2-deficient* osteoclasts exhibit defective bone resorption in vitro [80]. Furthermore, pharmacological inhibition of ARTD5 and ARTD6, which results in SH3BP2 accumulation, promotes osteoclast differentiation in vitro and bone resorption in vivo [81,89], findings that are consistent with accelerated in vitro osteoclastogenesis of osteoclast precursors lacking both ARTD5 and ARTD6 [78]. A recent study suggests that oral bacteria produce pathogen-associated molecular patterns (PAMPs), which in conjunction with danger-associated molecular patterns (DAMPs) released during the remodeling of the jaws, provide tissue-restricted bone lesions in cherubism. Decreased jaw remodeling with age leading to attenuated levels of DAMPs may underlie the reported regression of this disorder over time in the affected patients [90]. Thus, ARTD5 and ARTD6 function as negative regulators of osteoclast differentiation (Figure 2).

2.3. Role of SIRT6 in Osteoclast Differentiation

SIRTs are involved in the regulation of insulin secretion, gluconeogenesis, transcriptional regulation, and several other biological responses [91–95]. Relevant to this review are SIRT4 and SIRT6, owing to their MARylation activity that targets numerous proteins including glutamate dehydrogenase and ARTD1 [91,96–98]. SIRT6 also MARylates itself, a presumed mechanism of self-regulation [99]. Notably, SIRT6, but not SIRT4, has a strong deacetylase activity, a reaction where lysine deacetylation is

coupled to NAD^+ hydrolysis yielding O-acetyl-ADP-ribose, nicotinamide, and a deacetylated targeted protein [100–103].

Consistent with SIRT6 inhibitory effects on the transactivation of NF-κB, an important regulator of osteoclast development, overexpression of SIRT6 suppresses RANKL-induced OC formation in vitro and bone destruction in mice with collagen-induced arthritis [25,104–106]. Conversely, SIRT6 deficiency causes premature aging associated with increased osteoclastogenesis and low bone mass, or osteopenia associated with low bone turnover [107–110]. Moreover, myeloid-specific deletion of SIRT6 results in a decrease in estrogen receptor α protein levels and apoptosis of pre-osteoclasts, resulting in massive bone resorption during aging and following ovariectomy [111]. Accordingly, SIRT6 transgenic mice are protected from ovariectomy-induced bone loss. Mechanistically, SIRT6 deacetylates estrogen receptor α at K171 and K299, thereby preventing its proteasomal degradation. In contrast to these studies, SIRT6 reportedly forms a complex with Blimp1 to negatively regulate the expression of anti-osteoclastogenic genes such as V-maf musculoaponeurotic fibrosarcoma oncogene homolog B (Mafb), consistent with the increased bone mass and decreased osteoclast number in mice lacking SIRT6 in hematopoietic cells [112]. Conversely, retroviral-mediated overexpression of SIRT6 increases osteoclast formation [112]. Thus, SIRT6 regulates osteoclast differentiation, but the extent to which SIRT6-driven MARylation affects osteoclastogenesis is unclear given the deacetylase activity of this enzyme (Figure 2).

3. Osteoblast Differentiation

The osteoblasts differentiate from MSCs when exposed to growth factors such as bone morphogenetic proteins (BMPs), Wnts, Hedgehog, and Notch, which activate transcription factors such as RUNX2, osterix (OSX), and β-catenin [113]. Unlike osteoclastogenesis, osteoblast differentiation and function are regulated negatively by inflammatory signals, some of which are mediated by ARTs [114,115].

3.1. Role of ARTD1 in Osteoblast Differentiation

Immunohistochemical analysis of human bone samples shows that ARTD1 is mostly expressed in osteoblasts in the areas of new bone formation, to a lesser extent in osteoclasts, while no positive staining is detected in osteocytes, suggesting a role for ARTD1 in bone formation [116]. Poly-ADP-ribose (PAR) motifs are unexpectedly detected by nuclear magnetic resonance (NMR) and immunostaining in the bone extracellular matrix, mostly in the calcifying region of the growth plate, but to a lesser degree in the adjoining nonmineralized hypertrophic cartilage [117]. Thus, PAR units, which may be released during cell necrosis, are potentially implicated in bone matrix calcification. Earlier studies using human MSCs and SAOS-2 cells show that during osteoblast differentiation, hydrogen peroxide activates ARTD1 and promotes osteoblastogenesis via activation of the p38 MAPK pathway [118–120]. Consistent with its bone anabolic actions, the recruitment of ARTD1 by the long non-encoding RNA (lncRNA) STEEL results in increased angiogenesis and fracture healing [121]. Furthermore, the ARTD inhibitor PJ34 suppresses osteogenic differentiation of murine MSCs, but does not affect chondrocyte or adipocyte differentiation [122]. Thus, ARTD1 promotes osteoblast differentiation under physiological conditions. However, ARTD1 also interacts with NF-κB in mediating TNF-induced suppression of phosphate-regulating gene with homologies to endopeptidases on the X chromosome (Phex), whose important functions in bone mineralization include the inhibition of the expression of the hypophosphatemic fibroblast growth factor 23 (FGF23) [123,124]. Thus, while ARTD1 favors osteogenesis in homeostatic conditions (Figure 3), it may compromise this process in inflammatory states.

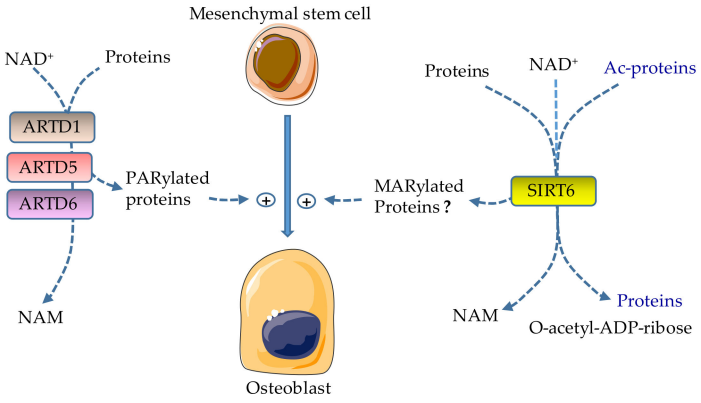

Figure 3. Effects of ADP-ribosylation on osteobast formation. ARTD1, ARTD5, and ARTD6 catalyze the attachment of ADP-ribose polymers from NAD^+ to target proteins (PARylation), releasing nicotinamide (NAM) in the process; their activities promote osteoblast differentiation. SIRT6 promotes osteoblast development; however the effects of MARylation driven by SIRT6 in this process are not clear because this enzyme also has deacetylase activity. Lysine deacetylation is coupled to NAD^+ hydrolysis, yielding a deacetylated targeted protein, O-acetyl-ADP-ribose, and NAM. Ac, acetyl.

3.2. Role of ARTD5 and ARTD6 in Osteoblast Differentiation

ARTD5 and ARTD6 PARylate and destabilize AXIN, a negative regulator of the critical osteogenic Wnt/β-catenin signaling pathway [125]. Bone formation is impaired both in vivo and in vitro in *Sh3bp2*-deficient cells through mechanisms involving the tyrosine kinase ABL, and the transcription factors TAZ and RUNX2 [80,126]. The inhibitors of ARTD5 and ARTD6 enhance in vitro osteoblastogenesis as the result of accumulated SH3BP2, promote nuclear translocation of ABL, TAZ, and RUNX2, but they paradoxically decrease bone mass in mice associated with an increased number of osteoclasts [81]. Thus, by stabilizing AXIN and SH3BP2, the inhibitors of ARTD5 and ARTD6 have the potential of inhibiting osteogenesis (Figure 3) and inflicting substantial damage to the skeleton.

3.3. Role of SIRT6 in Osteoblast Differentiation

SIRT6-deficient mice exhibit stunted growth as a result of abnormal development of the growth plate and impaired bone formation [108–110,127]. This phenotype is consistent with the plethoric actions of this enzyme. Indeed, SIRT6 regulates the expression of RUNX2 and OSX through deacetylation of H3K9; its deficiency is associated with hyperacetylation of H3K9 at the promoter of dickkopf-related protein 1 (Dkk1), a potent negative regulator of osteoblastogenesis [110]. SIRT6 also modulates the expression of the components of BMP signaling, actions that are p300/CBP-associated factor (PCAF)-dependent [128]. Finally, SIRT6 promotes osteogenic differentiation of rat bone marrow MSCs partially via suppression of NF-κB [129]. Thus, the actions of SIRT6 are pro-osteogenic osteoblastogenesis. However, given the importance of protein deacetylation in osteogenesis, a function that is also carried out by SIRT6, the role of MARylation mediated by this enzyme in this process is unclear.

4. Adipocyte Differentiation

Bone marrow adiposity and visceral fat are implicated in the pathogenesis of bone diseases such as osteoporosis [130,131]. Excessive differentiation of MSCs towards adipocytes in conjunction with the secretion of adipokines (e.g., adiponectin) and cytokines (e.g., IL-6) adversely impact bone metabolism. The adipogenic differentiation program of MSCs is controlled by transcription factors such as CCAAT/enhancer binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ) [132,133].

Role of ARTD1 in Adipocyte Differentiation

ARTD1 activity drops for several hours during the early phase of preadipocytes 3T3-L1 cell differentiation into adipocytes before returning to baseline levels and subsequently reaching higher levels, presumably as a result of chromatin modifications [134]. Studies using stromal cells from the fat pads of ARTD1-deficient mice show that the loss of this enzyme is associated with impaired adipocyte function and differentiation [135]. Accordingly, when fed with a high-fat diet, *Artd1* mice develop hepatosteatosis and dysregulated glucose metabolism. Using the preadipocyte 3T3-L1 cells, this group further demonstrates that ARTD1 is recruited to the promoters of *PPARγ2* and its target genes such as *CD36* and *aP2* in a PAR-dependent manner, responses that correlate with decreased histone marks of repressed chromatin (H3K9me3), while marks of active chromatin (H3K4me3) are increased [136]. However, studies based on a different mouse line suggest that lack of ARTD1 increases energy expenditure through SIRT1 activation [137], findings that are consistent with the browning of primary white adipocytes in vitro by olaparib, an inhibitor of ARTD1 and ARTD2 [138]. Other studies also show that ARTD1 PARylates C/EBPβ, thereby inhibiting its DNA binding and transcriptional activities, and ultimately, adipogenesis [139]. Thus, ARTD1 plays various roles in the differentiation of adipocytes, acting at different stages to promote or inhibit this process.

5. Therapeutic Implications

ARTs are novel and promising targets for cancer therapies. Numerous studies have shown that various small-molecule inhibitors of ARTDs are efficacious against various cancers, including ovarian cancer, breast cancer, colon cancer, lung cancer, prostate cancer, hepatocellular carcinoma, osteosarcoma, and chordoma [140–151]. More importantly, the US Food and Drug Administration has approved three different ARTD inhibitors, olaparib, niraparib, and rucaparib for the treatment of BRCA1- or BRAC2-mutated ovarian cancers. Considering the crucial role that ARTDs play in the pathogenesis of acute tissue injury or periodontitis, some of these drugs may be indicated for the treatment of inflammatory osteolysis. However, pre-clinical evidence indicates that genetic or pharmacological inhibition of ARTD1 or ARTD5 and ARTD6 causes bone loss, a high-risk factor for fracture. Therefore, comprehensive translational studies may help understand the extent to which ARTD inhibitors may adversely affect the skeleton.

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Conflicts of Interest: G.M. is a consultant for Aclaris Therapeutics, Inc. Other authors declare no conflict of interest.

Abbreviations

ADP: adenosine diphosphate; ARH, ADP-ribosyl hydrolase; ART, ADP-ribosyltransferase; ARTD, diphtheria toxin-like ART; ARTC, cholera toxin-like ART; Blimp1, B lymphocyte induced maturation protein 1; BMPs, bone morphogenetic proteins; C/EBPα, CCAAT/enhancer binding protein α; DAMPs, danger-associated molecular patterns; Dkk1, dickkopf-related protein 1; IL-1, interleukin-1; lncRNA, long non-encoding RNA; Mafb, V-maf musculoaponeurotic fibrosarcoma oncogene homolog B; MAPK, mitogen-activated protein kinase; MARylation, mono-ADP-ribosylation; M-CSF, macrophage colony-stimulating factor; MSC, mesenchymal stem cell; NFATc1, nuclear factor of activated T cells cytoplasmic 1; PAMPs, pathogen-associated molecular patterns; NAM, nicotinamide; NLRC4, NLR, CARD containing 4; NLRP3, NOD-like receptor family (NLR), pyrin domain containing 3; PARG, poly(ADP-ribose) glycohydrolase; OSX, osterix; PAR, poly-ADP-ribose; PARP, poly(ADP-ribose) polymerase; PARylation, poly-ADP-ribosylation; PCAF, p300/CBP-associated factor; Phex, phosphate-regulating gene with homologies to endopeptidases on the X; PM, post-translational modification; PPARγ, peroxisome proliferator-activated receptor γ; RANKL, receptor activator of NF-κB ligand; SH3BP2, SH3 domain-binding protein 2; SIRT, sirtuin; TARG1, terminal ADP-ribose protein glycohydrolase 1; TNF, tumor necrosis factor.

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