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Poly(ADP-ribose), *adherens junctions*, vinculin and the actin cytoskeleton: Current evidence, future perspectives and implications

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Abstract: Poly(ADP-ribose) (PAR) is a highly negatively charged polymer. PAR is synthesized by poly(ADP-ribose) polymerases (PARPs) and is involved in the assembly and stabilization of macromolecular complexes. Here, the presence and putative roles of poly(ADP-ribosyl)ation (PARylation) associated to *adherens junctions* (AJ) and the actin cytoskeleton in epithelial and Schwann cells, is reviewed. The hypothesis generated by analogy, stating that PAR is associated to AJ in other cell types, is postulated. According to this hypothesis, PAR associated to *puncta adherentia* in chemical synapses would participate in plasticity, learning and memory. In turn, PAR associated to *fascia adherens* in cardiomyocytes, would affect heart beating. PARP inhibitors are currently under development and clinical testing. Basic research in different tissues will probably influence their clinical uses.

An Introduction to Poly(ADP-ribose) (PAR)

Poly(ADP-ribosyl)ation (PARylation) is a biochemical reaction consisting on the synthesis of a linear or branched polymer called poly(ADP-ribose) (PAR), comprising up to 400 ADP-ribose monomers. PAR is covalently bound to proteins as a posttranslational modification, or to DNA (Matta *et al.*, 2020). With two negatively charged phosphates per unit and substructures that can be recognized by selected protein domains-such as Macro, WWE, RNA recognition motif (RRM) or PBM-, PAR can be regarded as a "glue" that facilitates assembly and stabilization of certain macromolecular complexes (Hottiger, 2015; Leung, 2014). Although PAR remained unnoticed until 1963 (Chambon *et al.* 1963, reviewed in Kraus, 2015), it is involved in several cellular processes. Moreover, PAR metabolism displays alterations in several inflammatory pathologies including diabetes, cardiovascular disease, infections, autoimmune disease, cancer and neurodegeneration (Bai, 2015; Cerboni *et al.*, 2010; Masutani *et al.*, 2005; Strosznajder *et al.*, 2012; Virag, 2002).

PARylation is catalyzed by four enzymes: PARP-1, PARP-2, tankyrase-1 (TNKS-1) and tankyrase-2 (TNKS-2). PARP-1/2 and TNKS-1/2 belong to a larger molecular family (PARP family, or ARTDs) that does also include inactive members-probably playing regulatory roles through substrate competition-, as well as intracellular enzymes with mono(ADP-ribosyl)ating activity (Lüscher *et al.*, 2022). PARP-1, the canonical PARP, has been deeply involved in all nuclear functions, including chromatin structure modulation, transcriptional regulation, imprinting (Lafon-Hughes *et al.*, 2008), DNA repair and cellular response to stress. PARP-1 and PARP-2 have partially overlapping functions (Bai, 2015).

TNKS-1/2 lack the DNA binding domain of PARP-1/2. They have an Ankyrin binding domain, present in several sub-membrane region proteins, instead (Chi and Lodish, 2000). TNKS is required during mitosis, colocalizes with the Golgi system (Smith and de Lange, 1999; Wahlberg *et al.*, 2012), and is involved in cell junction assembly and Wnt/Axin/β-catenin signaling (Bao *et al.*, 2012; Chi and Lodish, 2000; Yeh *et al.*, 2006).

Current Evidence Associating PAR with *Adherens Junctions* (AJ), Vinculin and Actin Microfilaments

TNKS–dependent PARylation of VCL vs. epithelial cell morphology

In epithelial cells, some actin microfilaments are anchored to cell-matrix integrin-harboring focal adhesions (FA) while a characteristic subcortical actin ring is bound to a cadherin and catenin-rich cell-cell *adherens junction* (AJ) belt or

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zonula adherens (Domke *et al.*, 2014; Niessen and Gottardi, 2008). Some zonula AJ proteins, like β-catenin, are called nuclear and AJ complexes proteins (NaCos) because they help coordinate cell shape and polarity with cycling dynamics, alternatively being integral components of zonula AJ complexes or acting as transcription factors (Aho *et al.*, 2009; Balda, 2003). A relevant actor in anchoring the actin cytoskeleton to both *zonula* AJ and FA is Vinculin (VCL) (Bays and DeMali, 2017). Being involved in mechanosensing, VCL recruitment to *zonula* AJ is force-dependent (Le Duc *et al.*, 2010). VCL regulates cell-cell contact stability (Seddiki *et al.*, 2018) and facilitates mechanical coupling between actin microfibers and the extracellular matrix (Angulo-Urarte *et al.*, 2020). Interestingly, VCL regulates epithelial cells characteristics including cell polarity, cycling, adhesion and migration (Coll *et al.*, 1995; Maddugoda *et al.*, 2007; Pal *et al.*, 2019; Peng *et al.*, 2010; Raz and Geiger, 1982; Sumida *et al.*, 2011; Xu *et al.*, 1998a; Xu *et al.*, 1998b). VCL has also been detected in the nucleus, indicating that it might be a NaCo (Flachs *et al.*, 2019; Hwang *et al.*, 2017).

Epithelial cells harbor a PAR belt, detected by immunoctytofluorescence under confocal microscopy (ICF-CFM). The PAR belt colocalizes with *zonula* AJ, VCL and the subcortical actin ring. In contrast, FA display no PARylation signal (Lafon-Hughes *et al.*, 2014). Therefore, the VCL pool PARylated in epithelial cells extracts, would correspond to VCL bound to *zonula* AJ (Vilchez Larrea *et al.*, 2021).

The PAR belt is lost under treatment with cytochalasin D, an actin polymerization inhibitor (Lafon-Hughes *et al.*, 2014). Conversely, in the presence of TNKS inhibitors, neither the PAR belt nor the subcortical actin ring are assembled, while cell shape becomes more irregular, mesenchymal-like (Lafon-Hughes *et al.*, 2014; Vilchez Larrea *et al.*, 2021). VCL harbors a TNKS binding motif (TBM) required to achieve TNKS-dependent PARylation. The overexpression of a chicken VCL gene carrying a point mutation in the TBM, unlike wt-VCL, induces a cell shape change reminiscent of an epithelial to mesenchymal transition (EMT) (Vilchez Larrea *et al.*, 2021). Accordingly, in an EMT model, under TGF-β induction of EMT, the PAR belt is lost together with epithelial markers, characteristic cell shape and low F-actin anisotropy (Schacke *et al.*, 2019). In the meantime, nuclear PAR increases. Conversely, a treatment with Olaparib, an inhibitor of PARP-1/2, diminishes nuclear PAR, preserves epithelial morphology/anisotropy and molecular markers, and restores the PAR belt, indicating the importance of the PAR belt and its close relation with the actin cytoskeleton (Schacke *et al.*, 2019). This work highlights the fact that Olaparib, approved as an anticancer drug following a synthetic lethality paradigm, may show effects beyond the promotion of cell death through DNA repair failure. Olaparib can deeply affect the cell morphological and functional phenotype, including the PAR belt, suggesting the existence of a crosstalk among nuclear PARPs and TNKS.

Schwann cells autotypic AJ regions are PARylated and total PAR distribution and quantity parallels F-actin

The presence of PAR associated to AJ-rich regions in non-epithelial tissues could be biologically meaningful. In fact, in peripheral nerves, Schwann cells harbor autotypical AJ that fix the successive myelin layers (Fannon *et al.*, 1995). Such autotypical AJ, with a molecular composition similar to epithelial *zonula* AJ (e.g., E-cadherin rich), are distributed in regions called paranodes (PN) and Schmidt-Lanterman incisures (SLI). Analysis of Schwann cells supported PAR presence in PN and SLI. Moreover, in a mice model of Charcot-Marie-Tooth demyelinating pathology, PAR distribution and quantity alterations parallel the F-actin changes (Lafon Hughes *et al.*, 2017). This work indicates that PAR is associated with autotypical AJ and the actin cytoskeleton. Moreover, it links PARylation and myelination.

Working Hypothesis

A role of VCL PARylation in synaptic plasticity, learning and memory?

Fig. 1 highlights the analogous structure of AJ complexes from different cell types in spite of their dissimilar subcellular distribution patterns. The figure depicts the core structure of AJ (Fig. 1A), the epithelial cells with their belt (Fig. 1B), Schwann cells with AJ at autotypic junctions at PN and SLI (Fig. 1C), neuronal synapses with synaptic clips called transynaptic *puncta adherentia* (Fig. 1D) and cardiomyocytes with *fascia adherentia* in their intercalated discs (Fig. 1E). Fig. 1 does not pretend to be exhaustive; it is just showing well-documented examples. PAR has been detected in epithelial *zonula adherens* and is Schwann cell PN and SLI. PAR detection in *puncta adherentia* and *fascia adherens*, with different implications, is envisaged.

In chemical synapses, transynaptic AJ complexes called *puncta adherentia* clip the presynaptic active zone (PRE) and postsynaptic density (POST) (Kilinc, 2018; Uchida *et al.*, 1996). Cadherins are involved in synaptic plasticity and long-term potentiation (LTP). Synaptic activity modulates synaptic adhesiveness (Bekirov *et al.*, 2002; Benson, 2000; Bozdagi *et al.*, 2004; Fields and Itoh, 1996; Tang *et al.*, 1998). Catenins do also regulate synapses. For example, upon depolarization, β-catenin relocation promotes synaptic structural and functional changes (Kilinc, 2018). VCL is required for neuronal mechanosensing (Wang *et al.*, 2021) and participates in synaptic plasticity (Liśkiewicz *et al.*, 2020). F-actin does also play a role in synaptic structure and function (Bucher *et al.*, 2020; Gentile *et al.*, 2022; Lavoie-Cardinal *et al.*, 2020; Zhang and Benson, 2001). To sum up, cumulative evidence indicates that *puncta* AJ, VCL, mechanical forces and the actin cytoskeleton play concerted crucial roles in synaptic establishment and plasticity. One wonders (i) whether PAR is associated to *puncta* AJ, and in such case, (ii) whether PARylation is involved in synaptic plasticity, LTP, memory and learning. We cannot answer the former issue yet. Regarding the latter, independent evidence indicates that PARylation can be induced by depolarization or neurotrofin treatment (Homburg *et al.*, 2000; Visochek, 2005), and that LTP, memory and learning require PARylation (Berger *et al.*, 2018; Cohen-Armon, 2004; Goldberg *et al.*, 2009; Strosznajder *et al.*, 2012). To what extent nuclear PAR or *puncta* AJ-associated PAR contribute to the cited results, remains to be established. Thus, the presence of PAR associated with *puncta* AJ in chemical synapses is a reasonable working hypothesis. By

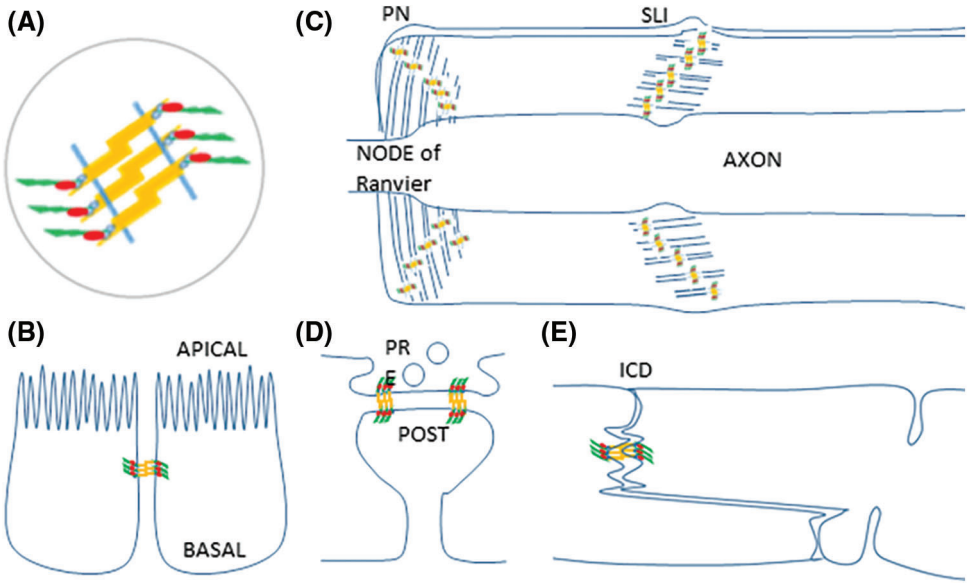

FIGURE 1. Examples of cell types where *AJ fundamental structure is conserved while AJ distribution varies*. (A) AJ share a common molecular structure. Two neighbor membranes are represented as *blue segments*. Cadherins (*yellow*) have an extracellular domain that mediates adhesion, a single pass transmembrane domain, and a cytoplasmic domain that interacts with catenins (*blue ovals*) to anchorage F-actin (*green*). VCL (*red*) is recruited to the AJ-actin cytoskeleton interphase to support tension. (B) *Zonula adherens* in epithelial cells. (C) Autotypic AJ in paranodes (PN) and Schmidt-Lanterman Incisures (SLI) in Schwann cells. (D) Transynaptic *puncta adherentia* in a neuronal chemical synapse, joining the presynaptic and postsynaptic components (E) *Fascia adherentia* in intercalated discs in cardiomyocytes.

analogy to epithelial AJ, TNKS involvement in the PARylation of VCL associated with *puncta* AJ is expected. Indeed, in primary hippocampal neurons, TNKS is detected in the soma and neurites, partially co-localizing with PAR signals. Moreover, TNKS inhibitor XAV939 suppresses neurite outgrowth and synaptogenesis (Mashimo *et al.*, 2022). It would be worth verifying the colocalization among *puncta* AJ, VCL, synaptic components, F-actin and PAR. If confirmed, it would also be tempting to analyze if there are changes in *puncta* AJ-associated PARylation associated to plasticity, LTP, learning and memory.

A role of VCL PARylation in cardiomyocytes?

VCL knockout results in brain and heart defects during embryonic development (Xu *et al.*, 1998a). Cardiomyocytes cell-cell AJ constitute the *fascia adherens*, located in intercalated disks (ICD). The *fascia adherens* is involved in mechanical coupling and reinforcement of cardiomyocytes, withstanding repeated cycles of actomyosin-mediated contractile force. VCL is a critical link to contractile actomyosin (Merkel *et al.*, 2019). Components of the *fascia* AJ including N-cadherin, α-E-catenin, β-catenin, and VCL play important roles in cardiac development, disease, and arrhythmias. In fact, cardiac-myocyte–specific VCL knockout mice display cardiac AJ/ICD abnormalities, leading to ventricular tachycardia and sudden death. VCL is necessary for preservation of ICD ultra-structure as well as cardiac function (Sheikh *et al.*, 2009). It is highly probable that PAR is present in *fascia* AJ, strengthening the junctions and participating in differentiation maintenance.

Future Perspectives and Clinical Implications

The presence of PAR associated to grouped AJ subject to high-tension forces and recruiting VCL is likely to have important structural, physiological and pathological relevance in contexts as different as epithelial cell phenotype maintenance, myelination by Schwann cells, synaptic plasticity, cardiac development and heart beating. PARP-1/2 and TNKS inhibitors are being actively developed and introduced to the clinic. Basic research regarding the effect of such inhibitors in different tissues (not limited to the ones here addressed) will likely lead to context-dependent restrictions and expansions in inhibitors clinical uses.

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