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Regulation of CD95/APO-1/Fas-induced apoptosis by protein phosphatases

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ABSTRACT

Triggering the CD95/APO-1/Fas receptor by CD95-L induces the assembly of the death-inducing signaling complex (DISC), which permits initiator caspases activation and progression of a signaling cascade that culminates in cellular apoptosis. Despite the CD95 receptor does not exhibit any kinase activity by itself, phosphorylation/dephosphorylation events seem important to regulate many aspects of CD95-mediated apoptosis. Here, we try to highlight particularly the importance of protein phosphatases in the modulation of the CD95 system.

1. The CD95/APO-1/Fas signaling pathway

Apoptosis is induced by the triggering of the tumor necrosis factor (TNF) superfamily of death receptors. These receptors are characterized by the presence of a protein–protein interaction domain (called death domain, DD) in their cytoplasmic tail. These are tumor necrosis factor receptor-1 (TNF-R1, also known as DR1, CD120a, p55 or p60), CD95 (also known as DR2, APO-1 or Fas), DR3 (also known as APO-3, LARD, TRAMP or WSL1), TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1, also known as DR4 or APO-2), TRAIL-R2 (also known as DR5, KILLER, or TRICK2), DR6, ectodysplasin A receptor (EDAR) and nerve growth factor receptor (NGFR) [1]. Binding of their respective ligand triggers the recruitment of a set of molecules transducing apoptotic and/or survival signals.

Amongst the death receptors, CD95 is one of the best-characterized members. CD95 is expressed in most tissues, and has been shown to induce apoptosis in lymphocytes, brain, pancreas and liver. Triggering of CD95 by its ligand (CD95-L) leads to the oligomerization of CD95 and the assembly of a typical multi-protein complex called death-inducing signaling complex (DISC) (Fig. 1) [2]. It has also been reported that CD95 self-associates as trimers before CD95-L binding via an extracellular domain called PLAD (pre-ligand association domain). Formation of pre-associated receptors is essential for downstream CD95 signaling [3,4]. The DISC formation allows the recruitment and activation of initiator

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Abbreviations: DISC, death-inducing signaling complex; PTP, protein tyrosine phosphatase; FAP-1, Fas-associated phosphatase-1; SHP-1, SH2-containing PTP-1 protein; PTP-1B, protein phosphatase-1B; PTEN, phosphatase and tensin homologue; DD, death domain; EGF, epidermal growth factor; FADD, Fas-associated death domain containing protein; *lpr*, lymphoproliferation; *gld*, generalized lymphoproliferative disorder; ALPS, autoimmune lymphoproliferative syndrome.

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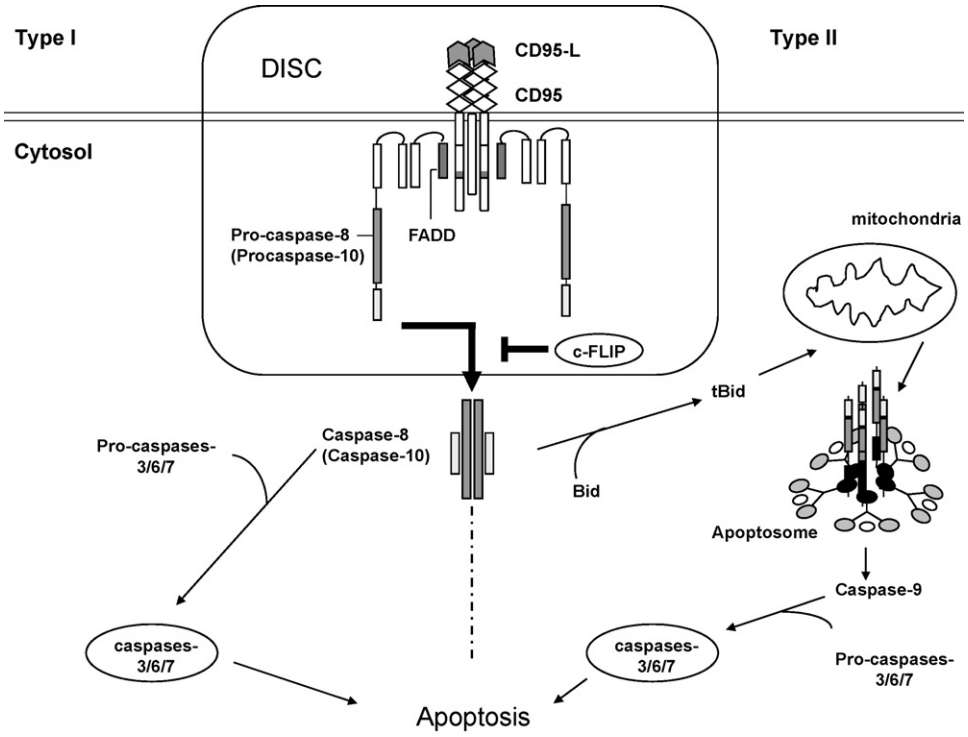

Fig. 1 – The CD95 signaling pathway. Binding of CD95-L to its receptor leads to the formation of the death-inducing signaling complex (DISC). In type I cells, CD95 triggering leads to strong caspase-8 activation at the DISC which bypasses mitochondria, resulting in direct cleavage of executioner caspases and *in fine* apoptosis (left side of the discontinued line). In type II cells, less caspase-8 is activated at the DISC and an amplification loop is required, involving tBid-mediated cytochrome *c* release from the mitochondria followed by the apoptosome formation (right side of the discontinued line). The resulting caspase-9 activation allows the cleavage of executioner caspases and cell death. Adapted from [21].

caspases (caspases -2, -8 or -10), mediated by the adaptor molecule FADD. FADD contains two protein–protein interaction domains (DD and DED) and links the receptor to initiator caspases through homotypic interactions [5–7]. The recruitment of procaspase-8 to the DISC leads to its activation through dimerization of monomeric zymogens and autocatalytic cleavage [8–10]. The caspase-8 prodomain remains at the DISC whereas caspase-8 active heterotetramer is released into the cytosol to propagate the apoptotic signal through activation of executioner caspases, namely caspases-3, -6 and -7. Besides caspase-8, caspases-2 and -10 are also found at the DISC but their role in the CD95-induced caspases cascade activation is still a matter of debate in the literature [7,11–15].

Two pathways of CD95 apoptosis signaling, depending on the amount of active caspase-8 generated at the DISC, have been described [16]. In type I cells, a large quantity of active caspase-8 can directly cleave procaspase-3, starting a caspases cascade that bypasses the mitochondria (Fig. 1). By contrast, type II cells show a reduced DISC formation and depend on an amplification loop *via* the mitochondria. Apoptosis in these cells is dependent, at least in part, on the cleavage of the BH3-only pro-apoptotic Bcl-2 homologue Bid. Truncated Bid (tBid) then migrates to the mitochondria where it induces the release of cytochrome *c* into the cytosol [17]. This is followed by the formation of the apoptosome. This complex, composed of cytochrome *c*, APAF-1 and dATP permits the recruitment and activation of the typical initiator caspase of the mitochondrial apoptotic pathway, namely caspase-9 [18].

One major regulator of CD95-mediated apoptosis at the DISC level is cellular FLIP (c-FLIP). It contains tandem DEDs and a caspase-like domain. The inhibition of apoptosis by c-FLIP was shown to be mediated by its recruitment and cleavage in the DISC instead of procaspase-8, preventing the cleavage and activation of the functional enzyme and the subsequent transduction of apoptotic signal (Fig. 1) [19].

CD95-induced apoptosis plays an important role in the homeostasis of many cell types in the human body. It is involved in the down-regulation of the immune response *via* the so-called activation-induced cell death (AICD), characterized by the death of preactivated lymphocytes upon the restimulation of their T cell receptors [20,21]. In mice, *lpr*, lpr^{cg} and *gld* mutations are associated with defects in the CD95 pathway, accounting for autoimmunity, abnormal accumulation of T and B cells and lymphadenopathy [22]. The *lpr* mutation is associated with the insertion of a retrotransposon into intron 2 of the CD95 gene, leading to an important decrease in CD95 surface expression [23]. Lpr^{cg} is a single point mutation within the death domain of CD95, thereby abrogating downstream signaling [24]. Finally, the *gld* mutation causes the expression of a defective CD95-L [25]. In human, mutation in *CD95* or *CD95-L* genes (or related molecules) can lead to an *lpr*-like pathology known as autoimmune lymphoproliferative syndrome (ALPS) [22]. CD95 is also expressed by various

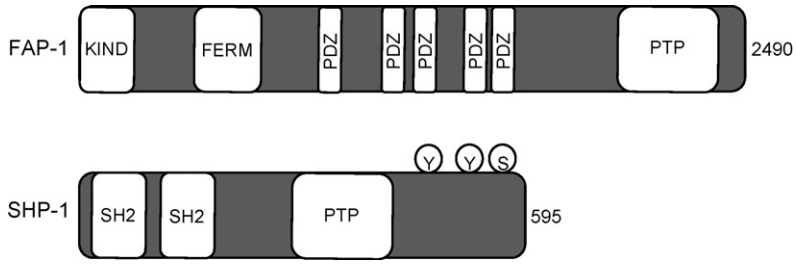

Fig. 2 – Structure of two CD95-interacting PTPs, FAP-1 and SHP-1. FAP-1 tyrosine phosphatase domain is located in the carboxy-terminal part of the protein. FAP-1 encompasses also several protein–protein interaction domains called KIND, FERM and PDZ. SHP-1 displays two SH2 domains in its amino-terminal part followed by a central catalytic domain. The carboxy-terminal tail of SHP-1 contains several phosphorylable residues such as tyrosines (Y) and serine (S). Amino acids number of each phosphatase is indicated at the right side of the picture.

epithelial cells. CD95-dependent apoptosis is implicated in the pathogenesis of liver injury induced by many noxes [26], and defective expression of CD95 is often described in solid tumors, thereby accounting for apoptosis resistance [27]. Finally, it was recently shown that CD95 mediates non-apoptotic functions [28].

2. Regulation of the CD95-dependent apoptosis by protein phosphatases

2.1. *Protein tyrosine phosphatases*

Tyrosine phosphorylation of proteins is achieved by protein tyrosine kinases (PTK). This reversible protein post-translational modification regulates many transduction pathways in eukaryotic cells, like those involved in embryogenesis, development, cell proliferation and motility. Protein tyrosine phosphatases (PTP) act by removing phosphates from tyrosine residues, thereby counteracting PTK effects [29,30]. PTPs contain a signature motif [I/V]HCXXGXXR[S/T] where the invariant cysteine residue is the nucleophile during catalysis and the arginine serves as phosphate binding [31]. Classical PTP are divided into two subgroups, the cytoplasmic (non-receptor) and transmembrane proteins, also called receptor PTP (RPTP) [32]. Here, we will present the reported effects of classical PTPs on CD95 signaling pathway, focusing our attention particularly on the early events of this pathway.

2.1.1. *FAP-1*

FAP-1 (for Fas-associated phosphatase-1, also called PTPL1, PTP-BAS or PTP1E) is a non-receptor PTP of 270 kDa encoded by the *PTPN13* gene. This huge protein contains a protein tyrosine phosphatase domain located at the extreme C-terminus part of the protein and several protein–protein interaction motifs in the N-terminus and central regions called respectively KIND, FERM and PDZ domains (Fig. 2) [33]. KIND is located at the extreme N-terminus and contains a kinase noncatalytic C-lobe domain showing homologies with the regulatory C-lobe of protein kinases, but lacking catalytic activity [34]. The functional role of this domain is yet unknown. The Four-point-one/Ezrin/Radixin/Moesin (FERM) domain follows the KIND domain. FERM domains are important mediators between plasma membrane receptors and cytoskeleton [35]. FAP-1 also contains five PDZ (PSD-95/*Drosophila* discs-large/Zonula occludens) domains which are located in the central region of the protein and are involved in the formation of supramolecular protein complexes [36]. The exhaustive description of FAP-1 interacting proteins is beyond the scope of this article and has been presented elsewhere [33,37]. FAP-1 was reported to directly interact with the cytoplasmic domain of human CD95 via its PDZ 2 and 4 domains [38-41]. FAP-1 binds the C-terminal 15 amino acids of CD95, and the deletion of these 15 amino acids enhances apoptosis induced by CD95-L [38,42]. The complementation of Jurkat T cells (which do not express FAP-1) with wt FAP-1, but not with a phosphatase inactive form, protects them from CD95-mediated apoptosis, suggesting that FAP-1 is involved in the negative regulation of the CD95 pathway [38]. However, this interaction does not seem to be evolutionary conserved, since the mouse CD95 does not interact with PTP-BL (the mouse homolog of FAP-1), and that PTP-BL does not inhibit CD95-induced apoptosis in mice [43]. Nonetheless, there is a clear correlation between the expression of FAP-1 and the survival of several human tumor models, including ovarian, colon, head and neck cancers, hepatocellular carcinoma, hepatoblastoma and pancreatic adenocarcinoma [41,44–49]. Accordingly, stable introduction of FAP-1 in FAP-1 negative pancreatic and melanoma cell lines or in squamous cell carcinoma of the head and neck was reported to inhibit CD95-mediated apoptosis [46,50,51]. FAP-1 is also important for the regulation of immune cells apoptosis. A down-regulation of FAP-1 mRNA was observed in IL-2-activated T cells, accounting for a higher sensitivity to CD95-induced apoptosis [52]. Enhanced apoptosis in T helper 1 (Th1) comparing to Th2 cells is due to unequal FAP-1 expression between these two populations [53]. In the same way, up-regulation of FAP-1 is responsible for the escape of HTLV-1 infected T cells from CD95-induced apoptosis [54]. At the molecular level, it appears that FAP-1 is able to regulate cell surface localization of CD95. Forced expression of FAP-1 increases the intracellular pool of CD95, and siRNA against FAP-1 up-regulates CD95 membrane expression [46,51]. Confocal microscopy studies revealed that FAP-1 is mainly associated with the Golgi complex where it appears to sequestrate CD95, thereby decreasing its membrane localization [50]. These observations suggest that tyrosine phosphorylation is involved in the localization of CD95 at the membrane. Indeed, it was shown that tyrosine kinases

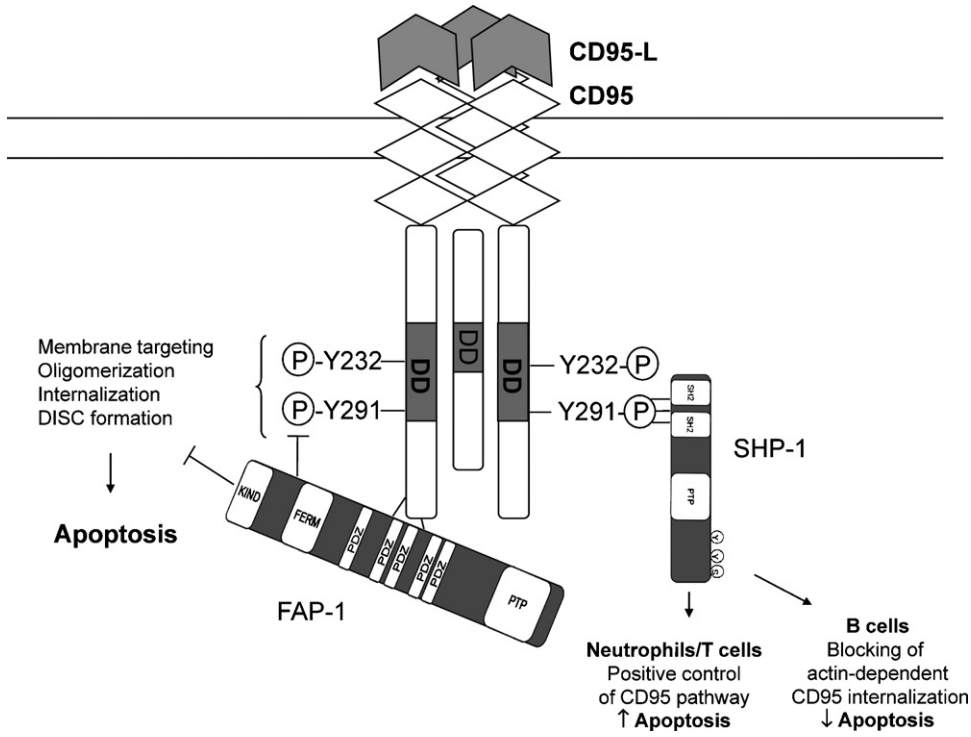

Fig. 3 – The role of FAP-1 and SHP-1 PTPs in the modulation of CD95-mediated apoptosis. Phosphorylation of Y232 and 291 in the death domain of CD95 is involved in membrane targeting, oligomerization and internalization of the receptor, followed by DISC formation and cellular apoptosis. FAP-1 was shown to down-regulate these events, likely by dephosphorylating CD95. SHP-1 was reported to bind CD95 Y291 and modulate oppositely the apoptotic response depending on the cell-type. DD: death domain.

inhibitors prevent CD95-induced apoptosis [55,56]. Moreover, CD95 interacts with $p59^{fyn}$ and $p56^{lck}$ tyrosine kinases, and this interaction enhances CD95-induced DISC formation and apoptosis [57,58]. Recently, it was nicely shown that CD95-L stimulation of hepatocytes (which do not express CD95 at the cell surface under basal conditions) induces a local production of reactive oxygen species resulting in a Yes-dependent activation of the EGF-R. This leads to the association between EGF-R and CD95 already in the cytosol and catalyses CD95 tyrosine phosphorylation [59,60]. This tyrosine phosphorylation is a prerequisite for CD95 membrane targeting, oligomerization and DISC formation [61]. Tyrosine phosphorylation occurs at positions Y232 and Y291 (also named Y216 and Y275[1]) in the death domain, and mutation of these residues to F or D prevents or increases the targeting of CD95 to the plasma membrane, respectively [51,61]. It has also been reported that intact CD95 Y291 is required for CD95L-induced internalization of CD95, a prerequisite for DISC assembly and apoptotic signal (Fig. 3) [62]. In that context, it is likely that FAP-1 regulates CD95 localization via tyrosine dephosphorylation of CD95. Indeed, a direct dephosphorylation of CD95 Y291 by FAP-1 was reported in astrocytoma cells (Fig. 3) [63]. All these results suggest that FAP-1 is a powerful negative regulator of CD95-induced apoptosis implicated in oncogenesis. This implies that FAP-1 expression must be tightly controlled in normal tissues to avoid oncogenic transformation. As already mentioned, FAP-1 transcription is down-regulated in activated T cells, and increased FAP-1 mRNA correlates with CD95 resistance in some leukemia cell lines [52,64]. The molecular events underlying the control of *PTPN13* (FAP-1) transcription has been recently clarified in myeloid cells. It was shown that the interferon consensus sequence-binding protein (ICSBP or IRF8) interacts with a *cis* element in the proximal *PTPN13* promoter and represses transcription during myeloid differentiation, accounting for an increased CD95 sensitivity [65]. Accordingly, ICSBP-deficient mice develop a myeloproliferative disorder [66].

2.1.2. *SHP-1*

SHP-1 (encoded by *PTPN6*, also called HCP, SH-PTP1) contains two tandem SH2 domains positioned at the N-terminus of the protein followed by a central catalytic region. The C-terminus region contains multiple phosphorylation sites and plays regulatory functions (Fig. 2) [67]. Mutations in the SHP-1 gene cause severe immunodeficiency accompanied by systemic autoimmune disease and chronic inflammation in mice homozygous for the recessive allelic mutation *motheaten* (*me*) or *viable motheaten* (me^{v}) on chromosome 6 [68,69]. This highlights the key role of this phosphatase in the negative regulation of cell function. Studies performed on *viable*

[1] There is some confusion regarding amino acid #1 for CD95: some people indicate as aa #1 methionine (M) of the signal peptide, while the others indicate arginine (R) from the mature protein without signal peptide. So, there is a shift of 16 aa if the full length CD95 is considered (V. Ivanov, personal communication).

motheaten mice reported that SHP-1 defect reduces lymphoid cells apoptosis induced by CD95, suggesting that SHP-1 is involved in the delivery of CD95-apoptosis signal in lymphocytes [70]. In neutrophils, SHP-1 binds a highly conserved Y_{291}xxL motif located in the death domain of CD95. Mutation of Y291 to A prevents SHP-1 binding upon CD95-L stimulation and inhibits cell death [71]. Since Y291 phosphorylation was shown to induce CD95 membrane targeting and internalization [61,62], one can speculate that SHP-1 would be involved in that process (Fig. 3). In the same way, it was recently shown that SHP-1 binds caspase-8 via an Y_{310}xxL motif located in the pro-domain of caspase-8, and Y310F mutation disrupts this interaction. In neutrophils, caspase-8 is basally tyrosine phosphorylated on Y397 and 465, and its dephosphorylation by SHP-1 results in its activation and progression of the apoptotic cascade [72]. These two observations suggest that SHP-1, on the contrary of FAP-1, controls positively the CD95 pathway. However, discrepant results were obtained. Hepatocytes apoptosis remained unchanged in me^v mice compared to wt mice, highlighting some cell-type specificities in SHP-1 pro-apoptotic activity [70]. On the contrary to me^v mice, no involvement of SHP-1 in CD95-mediated T cell death was reported using *me* mice [73]. The *me* mutant carries a deletion of one base-pair in the *SHP-1* gene, resulting in the absence of SHP-1 protein. On the contrary, me^v mice express two variants of the SHP-1 protein lacking phosphatase activity [68,69,74]. The discrepancy between results obtained with *me* versus me^v mice is still unexplained, even if it is attractive to speculate that SHP-1 inhibits the CD95 pathway independent of its phosphatase activity. In B cells, recent results reported that SHP-1 plays a negative role in CD95-induced apoptosis by blocking actin-dependent CD95 internalization, a prerequisite for DISC formation [75]. Therefore, the exact involvement of SHP-1 in the CD95 pathway is still matter of debate in the literature, and appears to be highly cell-type specific (Fig. 3).

2.1.3. PTP-1B

PTP-1B (encoded by *PTPN1*) contains an N-terminal catalytic domain followed by tandem proline-rich motifs and a small hydrophobic endoplasmic reticulum-targeting sequence at its C-terminus [76]. PTP-1B modulates various growth factors-induced signaling pathways by dephosphorylating receptors, such as insulin, IGF-1, EGF, PDGF and erythropoietin receptors [77-80]. Particularly, PTP-1B has a crucial role in negatively regulating insulin signaling, since PTP-1B deficient mice have increased insulin sensitivity and obesity resistance [81]. It was also recently reported that PTP-1B deficiency protects against liver apoptosis and fulminant hepatic failure induced by CD95, suggesting that PTP-1B is also a key modulator of the CD95 pathway [82]. PTP-1B deficient mice exhibit no caspase-8, -9 and -3 cleavage upon injection of CD95 antibody due to elevated anti-apoptotic proteins such as $FLIP_L$, ERK1/2 and NF-κB. The HGF/Met receptor, a potent hepatoprotective molecule, was also found hyperphosphorylated in PTP-1B KO mice, accounting for CD95-resistance. It is noteworthy that, despite the ubiquitous PTP-1B expression, resistance to CD95-apoptosis is limited to hepatocytes. Indeed, thymocytes from PTP-1B KO mice exhibit equal response to CD95-induced apoptosis when compared to wt mice [82].

2.2. Protein serine/threonine phosphatases

The protein serine/threonine phosphatases superfamily is divided into two subgroups. The phospho protein phosphatases (PPP) group includes notably types 1, 2A, 2B, PP4, PP5, PP6 phosphatases. Protein phosphatases magnesium-dependent (PPM) require Mg^{2+} or Mn^{2+} for their activity and comprise notably PP2C [83,84]. The involvement of serine/threonine phosphatases in the CD95 pathway is poorly known. Using pharmacological inhibitors, it has been shown that inhibition of PP1 and PP2A suppresses CD95-induced apoptosis by preventing DISC formation [85,86]. Even if the exact molecular mechanism is unknown, it appears that an increased MAPK/ERK activity would account for apoptosis resistance [86]. In neutrophils, PP2A regulates apoptosis by dephosphorylating both the pro-survival p38 MAPK and caspase-3, a p38 substrate. Since phosphorylation of caspase-3 impairs its activity, PP2A appears to promote neutrophils apoptosis. Accordingly, a rapid increase in PP2A activity is observed upon spontaneous or CD95-L-induced neutrophils apoptosis [87,88]. Protein serine/threonine phosphatases are also implicated in the control of the mitochondrial apoptosis pathway [89–91].

2.3. Lipid phosphatases

2.3.1. PTEN

PTEN is a lipid phosphatase whose major substrate is phosphatidylinositol-3,4,5-triphosphate (PIP3). Upon growth factors, cytokines or antigen stimulation, PIP3 is generated by the phosphoinositide-3-kinase (PI3K), thereby recruiting and activating the downstream kinase Akt through PDK1-mediated phosphorylation. Akt is involved in multiple cellular functions, like proliferation, oncogenesis and anti-apoptosis [92]. By reducing the pool of PIP3, PTEN is involved in the negative regulation of the Akt pathway and thus suppresses tumorigenesis. PTEN is one of the most frequently mutated tumor suppressor in human cancer, and a large number of tumors exhibit reduced PTEN expression [93,94]. $Pten^{+/-}$ mice develop lymphoproliferative disorders similar to those observed in *lpr* and *gld* mice, and lymphocytes from these mice are unresponsive to CD95-mediated apoptosis [95]. In long-term activated T cells (which are resistant to CD95-mediated apoptosis), increased phosphorylation of Akt due to the loss of PTEN expression accounts for a reduced DISC formation [96]. In the same way, T cells expressing active Akt are resistant to CD95-induced apoptosis due to impaired recruitment of caspase-8 to the DISC [97]. The underlying mechanisms are yet unknown. It thus appears that PTEN plays a key role in the modulation of the CD95 pathway through the control of Akt activation.

3. Conclusion and perspectives

We tried here to briefly summarize and highlight the key role played by protein phosphatases in CD95-mediated apoptosis. Among the whole family of protein phosphatases, PTP are incontestably the most important regulators of CD95 signaling. Indeed, tyrosine phosphorylation of CD95 is important to

regulate many signaling events, including CD95 membrane localization, oligomerization, internalization and subsequent DISC formation. Dephosphorylation of CD95 should thus have important biological functions, highlighting the role of PTP in CD95-dependent apoptosis. Even if strong biochemical evidences are lacking, it is likely that the FAP-1 and SHP-1 PTP regulate CD95 apoptosis through dephosphorylation of CD95 or related proteins. It was recently suggested that, depending notably of its subcellular localization, CD95 mediates non-apoptotic functions, like tissue regeneration and proliferation [28,62]. The involvement of PTPs in these processes is unknown and has been largely unappreciated. We suggest that reappraising the contribution of phosphorylation/dephosphorylation events in apoptotic or non-apoptotic functions of the CD95 system would permit a better understanding of its biology.

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