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Review

The complex understanding of Annexin A1 phosphorylation ☆

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ABSTRACT

Annexin A1 (ANXA1) is the first characterized member of the annexins superfamily. It binds the cellular membrane phospholipids in Ca^{2+} regulated manner. Annexin A1 has been found in several tissues and many physiological roles as hormones secretion, vesiculation, inflammatory response, apoptosis and differentiation have been shown. Its subcellular localization and binding with many partner proteins are altered accordingly with its physiological role. The Annexin A1 membrane localization is crucial for binding to receptors, suggesting a paracrine and juxtacrine extracellular action. Annexin A1 is subjected to several post-translational modifications. In particular the protein is phosphorylated on several residues both on the N-terminal functional domain and on the C-terminus core. Different kinases have been identified as responsible for the phosphorylation status of selective residues. The specific change in the phosphorylation status on the different sites alters ANXA1 localization, binding properties and functions. This review shows the physiological relevance of the ANXA1 phosphorylation leading to the conclusion that numerous and different roles of Annexin A1 could be associated with different phosphorylations to alter not only intracellular localization and bindings to its partners but also the extracellular receptor interactions.

Contents

1. Introduction

About 30 years ago, a 37 KDa protein was identified as a steroid-induced inhibitor of phospholipase activity with potential anti-inflammatory action. The protein was named lipocortin-1, lipomodulin, macrocortin or renocortin. Currently it is mostly known as Annexin A1 (ANXA1).

It is phosphorylated in vivo by protein tyrosine and serine–threonine kinases. During the years, many physiological functions

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related to ANXA1 activity, localization and modifications have been described. It was found that ANXA1 inhibits the phospholipase and it has been proposed that this activity could be regulated by its phosphorylation. In 1986 Pepinsky & Sinclair described the phosphorylation of Annexin A1 near its amino terminus by the protein tyrosine kinase activity of the epidermal growth factor receptor (EGF-R) [1]. This study has been updated and amplified by using recombinant Annexin A1 as a substrate for several putative protein kinases. The authors identified several phosphorylated residues by a combination of peptide mapping and sequence analysis and showed that recombinant pp60c-src phosphorylates Annexin A1 near its amino terminus, at tyrosine 21 (Tyr21). Also polyoma virus middle T/pp60c-src complex, recombinant pp50v-abl, and the EGF receptor/kinase phosphorylated the same tyrosine residue. It was also shown that serine 27 residue of ANXA1 is the primary site phosphorylated by protein kinase C (PKC). In the same study, the threonine 41 residue has been identified as a PKC substrate as well. The adenosine cyclic 3′,5′-phosphate dependent protein kinase A (PKA) phosphorylates ANXA1 in its carboxyl-terminal core at the threonine 216 residue (Thr216) [2]. In 1988 Schlaepfer & Haigler showed that PKC phosphorylated N-terminal peptides cleaved from ^{32}P-labeled AnnexinA1 contain phosphorylated threonine-24, serine-27, and serine-28 [3]. These studies raised the attention focus on the ANXA1 phosphorylation status and its possible role in regulation of the Annexin A1 functions (Fig. 1).

2. Initial studies of the phosphorylated Annexin A1 physiological roles

The annexins are a family of calcium-dependent, phospholipid-binding proteins [4]. Annexin A1, as the other annexins, is activated in its Ca^{2+}-bound conformation to bind the membrane phospholipids due to the exposure of its functional N-terminal domain. In contrast, the Ca^{2+}-free ANXA1 N-terminus is sterically hindered and not accessible [5]. Most of the ANXA1 functions are related to its ability to interact with cellular membranes. This interaction is reversible and regulated especially by post-translational modifications like phosphorylation. Tyrosine phosphorylation decreases the ANXA1 Ca2+ requirement for binding phosphatidylserine vesicles [6]. In 1992 Patte et al. published that treatment of synchronized HUVE endothelial cells with basic Fibroblast Growth Factor (bFGF) leads to tyrosine phosphorylation of Annexin A1. According to the published results, the effect of bFGF on ANXA1 phosphorylation occurs only during S phase of the cell cycle, suggesting a role of the FGF-receptor/kinase complex [7].

Wang et al. showed that phosphorylation of the N-terminal domain of ANXA1 by PKC induces chromaffin granules aggregation, responsible for the secretion of hormones. Their study started with the evidence that phosphorylation of serines of ANXA1 is induced by bovine chromaffin secretion [8]. According to their results, the phosphorylation by PKC of an unspecified residue leads to a strong inhibition of ANXA1 aggregative ability. The mechanism of action is probably related to the fourfold increase of Ca^{2+} requirement. The inhibitory effect was reversed by the phosphatase 2A mediated dephosphorylation of the Annexin A1. On the other hand, the ANXA1 phosphorylation by PKC was not able to interfere with the direct binding of ANXA1 to granules or phosphatidylserine and phosphatidylcholine vesicles, leaving unexplained the inhibitory effect on ANXA1. For this reason, the authors suggested, in an articulated discussion, an "unusual mechanism" of inhibition involving a sort of not yet established competition mechanism between the phosphorylated and unphosphorylated ANXA1 forms. Moreover the authors proposed a role of ANXA1 in regulation of hormones exocytosis via the ability to alter granules aggregation. [9] However, the process must be further characterized to drive a final conclusion.

At the same time it was shown that low concentrations (5 μM) of glycyrrhizin and a glycyrrhetinic acid derivative induced a protein kinase A (PKA) mediated ANXA1 phosphorylation. Curiously, higher concentrations of these compounds reverted completely the effect. As the natural compound examined showed anti-inflammatory activity, the conclusion and the speculation were that ANXA1 phosphorylation may have a role in the anti-inflammatory effects of the studied drugs [10].

Sawyer and Cohen showed that the ANXA1 phosphorylation is linked with EGF-R internalization suggesting that the endosomal EGF-R kinase may be involved in the phosphorylation of Annexin A1 [11]. Based on their results, it was shown by Futter et al. that ANXA1 is a substrate of EGF-R kinase in multivesicular bodies (MVBs, important for stimulated EGF-R internalization and sorting). Interestingly, phosphorylating a calcium-independent Annexin A1 converted it to a calcium-dependent form. The ANXA1 phosphorylation has been suggested being responsible for the MVBs inward vesiculation induced by EGF-R activation. The phosphorylated ANXA1 residue in this study is not shown. Other experiments were performed using both in vitro and cell culture approaches [12]. Summarizing the results and recent literature covering this topic, it can be concluded that ANXA1 is phosphorylated by EGF-R after internalization via the multivesicular bodies. This phosphorylation is not calcium-dependent but the phosphorylated Annexin A1 binds the phospholipids in a calcium-dependent manner.

Protein Kinase C (PKC) catalyzed phosphorylation of Annexin A1 and 2 in cultured rat mesangial cells in vitro required presence of Ca^{2+} and phospholipids. However, mere phospholipids were not sufficient to support the phosphorylation. In the experiments performed in vivo on ^{32}P-labeled mesangial cells, the ANXA 1 phosphorylation was increased by the addition of PKC activators as angiotensin II and phorbol myristate acetate (PMA). Moreover, a phosphoamino acid analysis, either by using two-dimensional chromatography or specific antiphosphotyrosine antibody, revealed that phosphorylation occurs only on serine residues [13]. These results were updated and partially confirmed by a study performed on rat renal glomeruli and rat

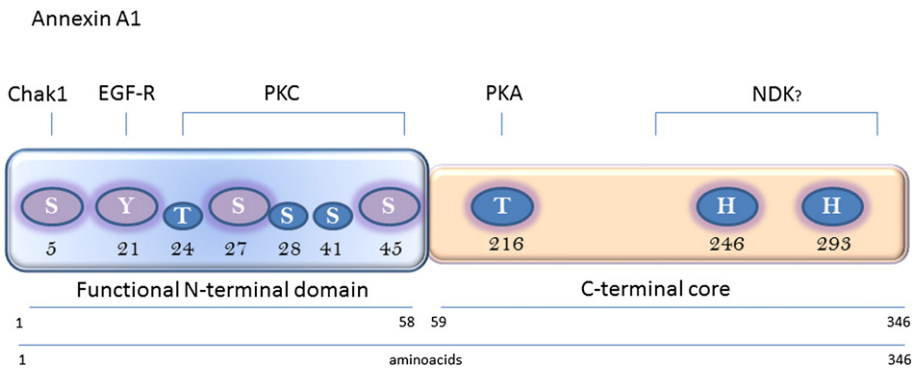

Fig. 1. Schematic representation of the target residues and principal kinases involved in ANXA1 phosphorylation. S, Y, H and T are respectively Serine, Tyrosine, Histidine and Threonine. Chak1 — TRPM7 Channel Kinase 1; EGFR — Epidermal Growth Factor Receptor; PKC — Protein Kinase C; PKA — Protein Kinase A.

glomerular mesengial cells labeled with ^{32}P-ATP. Treatment with angiotensin II, arginine-vasopressin and endothelin I stimulated Annexin A1 phosphorylation after 10 min from the treatment. Western blot analysis with an anti-phosphotyrosine antibody confirmed phosphorylation of tyrosine residues. This data suggested a possible role of Annexin A1 in mitogenic effect of angiotensin II, arginine-vasopressin, and endothelin [14].

Ohnishi et al. showed that the phosphorylation of Annexin A1 was markedly enhanced and it was associated with insulin secretion in rat pancreatic islets stimulated by a high concentration of glucose (20 mM). In this case, the phosphorylation occurred mainly on serine residues, as confirmed by using H-7, a potent PKC inhibitor [15]. In vitro, the phosphorylation of Annexin A1 by PKC was inhibited by Annexin V, which is not a PKC substrate [16]. Interestingly, the ANXA1 serine phosphorylation was responsible for a dramatic decrease of phospholipid vesicle aggregation. However, the ANXA1 phosphorylation did not alter its binding to the phospholipid vesicles [17]. It confirmed the idea that the phosphorylation of ANXA1 by PKC leads to inhibition of membrane fusion activity induced by ANXA1. On the other hand, another author in the same year, proposed the phosphorylation as the main activator of ANXA1 immunosuppressive activities [18]. However, no specific phosphorylation sites were described. It means that the phosphorylation of the protein does not necessarily cause its inactivation.

Even though the relevance of ANXA1 phosphorylation by PKC is widely accepted, it is important to remark that Farkas et al. published that in permeabilized granulocytes at supra-physiological Ca^{2+} concentrations, PKC bound to the cytoplasmic surface of the plasma membrane and was not actually accessible for the complex Ca^{2+}-ANXA1 [19].

3. Phosphorylation of the serine residue

In order to explain the role of the serine 27 phosphorylation, Porte et al. generated two ANXA1 mutants; S27E and S27A mimicking and preventing phosphorylation, respectively. Wild-type Annexin A1 and the S27A mutant protein showed the same calcium dependence for phospholipid vesicles aggregation. Adversely, the S27E mutant protein exhibited higher calcium requirement and a lower aggregation activity, confirming the phosphorylation inhibitory theory. By contrast, the liposome binding and self-association required identical calcium concentrations for the wild-type and both mutant proteins. This suggests that the phosphorylation of serine 27 residue could inhibit only one of these ANXA1 functions. Moreover, the authors have shown that the Ser27 phosphorylation induces a conformational change, which is probably related to the described membrane aggregation property [20].

4. Phosphorylation of the tyrosine residue

Huang et al. published the first results about in vitro experiments involving the EGF kinase activity in the phosphorylation of a 35 kDa PLA2 inhibitor protein, recognized as Annexin A1 [21].

Years later Salles et al. showed that growth factors and cytokines, including epidermal growth factor, insulin, pp60v-scr, and angiotensin II, are able to induce rapid tyrosine phosphorylation of Annexin A1 in an osteoblast-like rat osteosarcoma cell-line. [22]. On the other hand, the relevance of ANXA1 phosphorylation was still not fully clear, even though a role of phosphorylated Annexin A1 in signal transduction was suggested. In fact, tyrosine residue of ANXA1 was efficiently phosphorylated within 10 min after exposition to hepatocyte growth factor (HGF) and it translocated to the membrane fraction of A549 lung carcinoma cells. As antisense ANXA1 oligonucleotides reverted the HGF induced cell proliferation, the authors suggested that the phosphorylation of Annexin A1 may function as a "signal amplifier" in processes where the HGF receptor tyrosine kinase is activated. The proposed mechanism of action is induction of the release of intercellular messengers (as PGE2) with pluripotent roles in cell proliferation, chemotaxis, and vascular remodeling [23].

Tyrosine phosphorylated Annexin A1 promoted a dose-dependent inhibition of Insulin Receptor (IR) auto-phosphorylation. This effect required phosphorylation of the ANXA1 N-terminal domain at Tyr21 residue and was specific for insulin-stimulated tyrosine kinase activity. These data underscore a specific interaction of IR with Annexin A1 [24].

Solito et al. correlated the expression of Annexin A1 with phospholipase A2 activity in U937 cells stimulated by PMA and LPS. They performed both a sense and antisense ANXA1 plasmid transfection and proposed that the endogenous non-phosphorylated form of Annexin A1 may act intracellularly to block the cytosolic PLA2 activity. The authors detected that only 10% of Annexin A1 is phosphorylated on tyrosine, suggesting that the phosphorylation is not required for this function [25]. de Coupade et al. have shown that ANXA1 expression and phosphorylation could be implicated in liver regeneration and tumorigenesis, either through modulation of cPLA (2) activity or EGF-R function. Both the expression and the phosphorylation of Annexin A1 were increased upon EGF-R activation and consequent cancer growth [26]. Interestingly, a study conducted by Croxtall et al., using a peptide library, showed that the EQEYV domain is essential but not sufficient for some of ANXA1 activities. The peptides containing the EQEYV domain affected PLA2 activity, arachidonic acid release and A549 human adenoma cell growth. The described domain is localized at the N-terminal region of Annexin A1 and contains only the phosphorylatable Tyr21 [27].

5. Phosphorylation of the histidine residue

With increasing interest in ANXA1 phosphorylation activity, other groups joined the topic and some of them suggested interesting but not anymore explored inputs. For example Muimo et al. suggested that Annexin A1 may act in intracellular signaling. They found a new phosphorylation site, at the histidine of the ANXA1 carboxyl-terminal core. This phosphorylation was regulated by cAMP and AMP but not cGMP. The hypothesized, but not characterized, kinase for phosphorylation of these residues was the nucleoside diphosphate kinase (NDK) [28]. The residues proposed by the authors are the His246 and His293, conserved in all the evaluated species.

6. TRPM7 channel-kinase (Chak1) and the Ser5 Annexin A1 residue

In 2004, a new kinase involved in ANXA1 phosphorylation has been identified by Dorovkov & Ryazanov. They studied the TRPM7 channel-kinase in mouse C2C12 cells. It is a bifunctional molecule consisting of a TRP ion channel fused to a protein kinase domain. TRPM7 was responsible for phosphorylation of the serine 5 (Ser5) residue [29]. In 2009, the study focused on an association between ANXA1 and TRPM7 confirmed the presence of a TRPM7/Annexin A1/Mg^{2+} complex, suggesting a novel pathway in bradykinin signaling, dependent on PKC and c-src [30]. Even though that pathway is not fully characterized, the same team that discovered the Ser5 phosphorylation of ANXA1 also reported crucial relevance of this modification for ANXA1 membrane binding and especially for the interaction between Annexin A1 and its known partner, the calcium binding protein S100A11 [31]. This interaction is biologically relevant, as the disruption of the Annexin A1/S100A1 complex increased cervical cancer HeLa cells migration and clonogenic growth via the EGF signaling alteration [32].

7. The subcellular phospho-Annexin A1 localization

A theory about the correlation between Annexin A1 phosphorylation and its intracellular localization emerged in 2000. The topic was revitalized when Yoshii et al. found ANXA1 in rat liver mitochondria and proved that the protein was phosphorylated on tyrosine residues

[33]. However, the mitochondrial localization has not been further investigated.

Meanwhile, ANXA1 implication in growth regulation, differentiation and apoptosis has been reported and further studies were performed. Studies in human embryonic kidney HEK293 cells focused on Annexin A1 cellular localization during PMA-induced mitogenic signal showed cleavage of Annexin A1 which then migrated into the nucleus. The PMA-induced nuclear translocation of ANXA1 was inhibited by the PKCdelta-specific inhibitor, rottlerin, indicating that PKCdelta plays a role in nuclear localization of cleaved ANXA1 [34]. Even more intriguing is that dexamethasone induces changes in phosphorylation and subcellular localization of Annexin A1, in A549 human adenocarcinoma cells. The ANXA1 tyrosine phosphorylated co-localized with EGF-R, and its amount was increased upon dexamethasone exposition. This effect was reached in few minutes after dexamethasone stimulation and was surprisingly completely reverted by RU486, a known glucocorticoid receptor inhibitor [35]. It has been suggested that the phosphorylated Annexin A1 migrates to the cell membrane in order to interact with EGF-R. This result paved the way to the following studies about the Annexin A1 membrane localization. Nevertheless it was confirmed that Annexin A1 directly binds EGF-R during its internalization, but the binding is not dependent on the phosphorylation of the ANXA1 N-terminus. In accord with these results, the binding between EGF-R and Annexin A1 seems to be mediated through the Ca^{2+} binding core domain [36].

8. The Ser27 phosphorylation and membrane localization

John et al. showed that PKC phosphorylates Annexin A1 and its activity is essential for both cellular export and biological activity of ANXA1 in anterior pituitary glands. The ANXA1 exported from the cells contains phospho-serines [37]. The phosphorylation of Annexin A1 on Ser27 is crucial for migration to cell surface. This topic has been deepened by Solito et al. in 2003 who published that dexamethasone induced signaling caused translocation of a serine phosphorylated-ANXA1 to the cytoplasmic membrane of human folliculostellate cells (PDFS). These results suggest that glucocorticoids induce rapid serine phosphorylation and membrane translocation of ANXA1 via a novel glucocorticoid receptor-dependent mechanism, which requires MAPK, phosphatidylinositiol 3-kinase and Ca^{2+}-dependent PKC pathway [38]. Lately it has been shown that dexamethasone is also responsible for ANXA1 tyrosine phosphorylation, but this modification is not crucial for the Annexin A1 membrane targeting [39]. It has been clearly shown that the phosphorylation of Ser27 ANXA1 residue and its migration to the cell membrane are implicated in hormones release. McArthur et al. published recently the regulatory effects of ANXA1 on hormones exocytosis. The authors focused on the release of adrenocorticotropin from a corticotroph-like cell lines mediated by glucocorticoids. They confirmed an essential role of phosphorylation of ANXA1 serines 27 and 45 in its translocation to the cell membrane and its inhibitory action on hormones secretion. Moreover, the authors showed that the Annexin A1-dependent inhibition of adrenocorticotrophin release involves an enhancement of actin [40]. The complex ANXA1 role in the regulation of endocrine function is reported in a review published in 2004 by John et al. [41] (Fig. 2).

By that time, the physiological roles of Annexin A1 have been better identified, which pointed to its important role in cell–cell communication in the host defense and neuroendocrine systems. In both systems its actions are exerted extracellularly. The exposure to LPS caused phosphorylation of Ser27 ANXA1 and its translocation to the cell membrane. The trafficking of Ser27 phospho-ANXA1 to the cell surface was dependent on activity of PI3-kinase and MAP-kinase. The serine phosphorylation was essential for the protein migration and an involvement of isoprenyl lipids in this mechanism was identified. The isoprenyl lipids

Table 1
Phosphorylation sites prediction by PredictProtein Server and relative involved kinases.

cAMP phosphor sites (PKA)	Protein Kinase C (PKC)	Casein Kinase 2 (CK2)
Thr 216 [2]	Thr 24 [3]	Thr 64
	Ser 27[3]	Thr 132
	Thr 70	Thr 136
	Thr 88	Thr 145
	Thr 95	Thr 172
	Thr 145	Ser 244
	Thr 226	Ser 302
	Thr 272	Thr 331

Phosphorylation sites prediction performed using PredictProtein Server [46] on whole amino acid sequence of Annexin A1. In gray the already described and referenced phosphorylation residues. The references are reported in [ ]. Thr and Ser are respectively for Threonine and Serine.

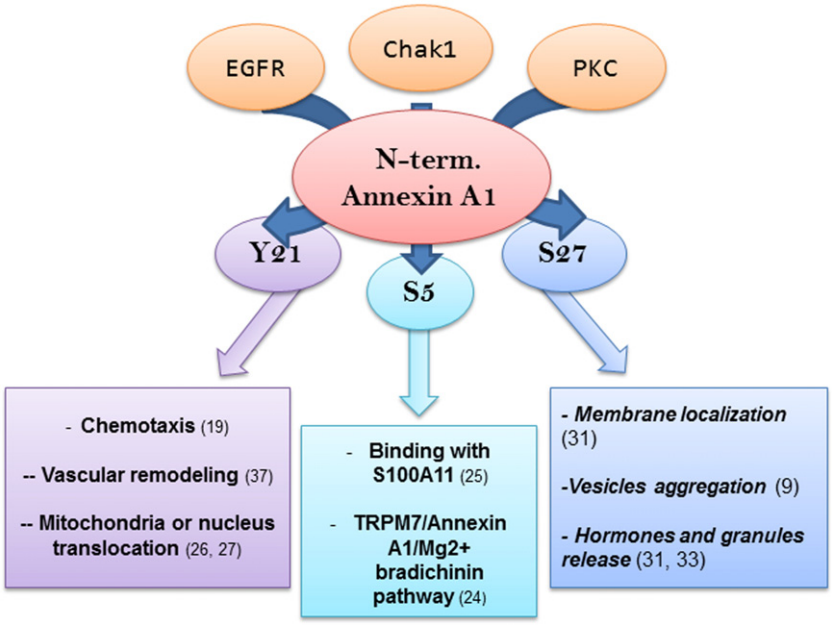

Fig. 2. Principal cellular effects of ANXA1 phosphorylation on the characterized residues.

Table 2
Phosphorylation residues and relative regulatory kinases.

Residue	Ser5 [29]	Tyr21 [1]	Thr24 [3] Thr41[1]	Ser27 [1]	Ser28 [3]	Ser45 [3]	Thr216 [2]	His246; His 293 [28]
Kinase	*TRPM7 channel kinase*	*EGF-R* pp60c-src IR	*PKC*	*PKC*	*PKC*	*PKC*	*PKA*	*NDK*
Localization	*N-term.*	*N-term.*	*N-term.*	*N-term.*	*N-term.*	*N-term.*	*C-Term. core*	*C-Term. core*

Schematic representation of phosphorylation residues reported in the review and relative regulatory kinases. Ser, Tyr, Thr and His are respectively for serine, tyrosine, threonine and histidine. N-term and C-term.core are abbreviations for the residue localization as N-terminal and C-terminal core. The kinases reported are TRPM7 (Chak1); Protein Kinase C (PKC); Protein Kinase A (PKA); Nucleoside diphosphate kinase (NDK); Epidermal Growth Factor Receptor (EGF-R); Insulin Receptor (IR); Tyrosin Protein Kinase (pp60 c-src). References are reported in [ ].

could target other proteins in the signal transduction cascade (for example transporters) or consensus sequences in ANXA1 [42].

9. Recent findings

In U937 cells, glucocorticoids treatment induced a rapid concentration-dependent activation of PKCalpha/beta and a Ser27 Annexin A1 phosphorylation. Phosphorylated ANXA1 was accumulated on the cell membrane and externalized inhibited thromboxane formation. Simultaneous use of glucocorticoids with cromoglycate-like drugs strongly increased Annexin A1 phosphorylation, migration and effect on thromboxane. It could be due to the inhibition of the phosphatase PP2A effect exerted by cromoglycates. The authors suggested the relevance of PP2A in a regulatory loop of Annexin A1 phosphorylation important to limit the ANXA1 release [43].

Intriguingly, in 2008 Petrella et al. have shown that U937, K562 and Jurkat leukemia cells exposed a Ser27 phosphorylated form of Annexin A1 on the cell surface, during HDAC inhibitor induced apoptosis. The phosphorylation and surface display appeared after 24 h of the treatment, implicating a late mechanism of action. The authors discussed the presence of Annexin A1 on the apoptotic cell surface both as an "eat me" and as putative pro-apoptotic signal [44]. Interestingly the phosphorylation of other residues has not yet been studied in the apoptosis context.

In 2009, a new interesting implication for phosphorylated Annexin A1 has been proposed by Côté et al. who showed that VEGF induces ANXA1 phosphorylation via LIM kinase1 and p38 pathways. The phosphorylation activates Annexin A1and it is involved in endothelial cell migration and tube formation [45]. Adopting a bioinformatics approach, it is also possible to predict new putative phosphorylation sites targeted by other kinases. For example the well-known PredictProtein Server [46] identifies residue substrates of the PKC and PKA, but not the phosphorylation depending by EFG-R. According to the server analysis some residues could also be substrates for Casein Kinase 2 (CK2), kinase not yet related to ANXA1 phosphorylation. The results obtained by PredictProtein Server are summarized in Table 1.

Finally in 2013 Caron et al. showed the relevance of Y21 phosphorylation for the ANXA1 stability. In fact the authors demonstrated that the tyrosine 21 phosphorylation is crucial for ANXA1 SUMOylation induced by EGF [47] (Table 2).

10. Conclusions

A research conducted on human pituitary adenomas showed that in all the patients the Annexin A1 was phosphorylated on the Ser27 residue. Only few patients resulted positive to the ANXA1 tyrosine phosphorylation and in all the cases its expression was weak [48]. Recently Annexin A1 has been described as a "double-face" protein, because of its numerous, diverse and sometime opposing functions. Associated to the well characterized FPR family receptors, it has been recently shown that ANXA1 triggers also other receptor activity, binding several partners. Its function may vary according to its cellular localization.

For this reason it is reasonable to consider the regulatory role of post-transcriptional modifications of ANXA1, including selective phosphorylation, as a key for the specific localizations, bindings and functions of Annexin A1. In this respect ANXA1 could be regulated similarly as numerous proteins and cytokines that change their mechanism of action according to the phosphorylation, triggering structural switch.

It is intriguing that more than 20 years of study of Annexin A1 phosphorylation have not provided detailed understanding of its role and mechanism of action. It is no doubt that the phosphorylation is necessary for ANXA1 regulation and activity. The hypothesis that phosphorylation of different ANXA1 residues could work as a switch-on/switch-off mechanism is captivating. It could explain the number of Annexin A1 physiological functions and it could also bring the attention to specific intracellular pathways and different receptor interactions. The complete understanding of the phospho-ANXA1 physiological involvements and the conformational changes due to the different phosphorylation targets could lead to new models and therapeutic approaches in treatment of cancer, inflammation, diabetes and neurodegenerative diseases.

Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

D'Acunto CW conceived, designed and wrote the review. Gbelcova H has been involved in drafting the manuscript and participated in its design and coordination. Festa M has been involved in revising the manuscript critically for important intellectual content. Tomas Ruml has made substantial contributions to conception and design and has given final approval of the version to be published. All authors read and approved the final manuscript.

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