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Review

# PLA2R1: Expression and function in cancer

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ABSTRACT

The phospholipase A2 receptor 1 (PLA2R1 or PLA2R) was isolated twenty years ago for its ability to bind several secretory phospholipase A2 proteins (sPLA2). Since its identification, it has attracted only a limited interest, mainly in the sPLA2 biology field, as it is viewed uniquely as a regulator of sPLA2 activities. Recent discoveries outline novel important functions of this gene in cancer biology. Indeed, PLA2R1 gain or loss of function experiments *in vitro* and *in vivo* shows that this receptor promotes several tumor suppressive responses including senescence, apoptosis and inhibition of transformation. Supporting a tumor suppressive role of PLA2R1, its expression decreases in numerous cancers, and known oncogenes such as HIF2α and c-MYC repress its expression. *PLA2R1* promoter methylation, a classical way to repress tumor suppressive gene expression in cancer cells, is observed in leukemia, in kidney and in breast cancer cells. Mechanistically, PLA2R1 activates the kinase JAK2 and orients its activity towards a tumor suppressive one. PLA2R1 also promotes accumulation of reactive oxygen species which induce cell death and senescence. This review compiles recent data demonstrating an unexpected tumor suppressive role of PLA2R1 and outlines the future work needed to improve our knowledge of the functions of this gene in cancer.



**Contents**



## 1. Introduction

The search for the receptor that binds the secretory phospholipase A2 (sPLA2) led to the identification of the secretory phospholipase A2 receptor 1 (PLA2R1 or PLA2R) about 20 years ago [33,35]. This receptor belongs to the C-type lectin superfamily and the mannose receptor family. The 4 receptors belonging to the mannose receptor family share a common structural organization, from its N-terminus; they are composed of a Cysteine rich domain (Cys-R), of a fibronectin type II domain (FNII) and of 8 or 10 C-type lectin domain (CTLD), a transmembrane domain and a short intracytoplasmic tail. Although these receptors share a similar organization, they display low amino acid identity, suggesting distinct functions of these receptors (Fig. 1) [17,48].

The sPLA2 catalyzes the hydrolysis of phospholipids and generates lysophospholipids and fatty acids, both being precursors of numerous

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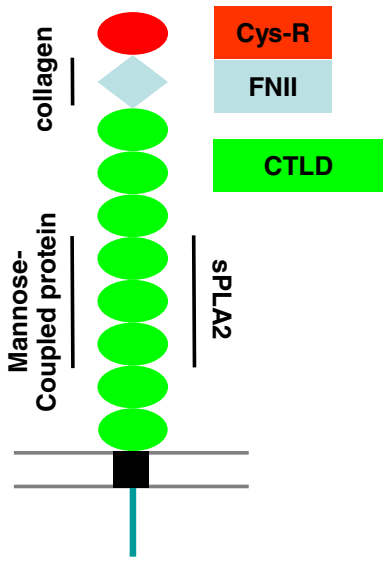


**Fig. 1.** PLA2R1 structure. PLA2R1 encoded a 180 kDa transmembrane protein displaying mannose receptor domain organization. Known interactions and domains involved are indicated.

lipid mediators. Yet the physiological roles of the binding of sPLA2 to PLA2R1 are unclear [42,43]. Importantly, only certain sPLA2 can bind PLA2R1, especially in humans [14]. PLA2R1–sPLA2 binding has been reported to inhibit sPLA2 catalytic activity and to promote their internalization and degradation [22,34,42,43]. Physiologically, this inhibitory role of PLA2R1 on sPLA2 results in a protective role in a model of lung inflammation in mice. Indeed, in that model, PLA2R1 decreases sPLA2 levels and eicosanoid production resulting in decreased inflammatory response [49].

Inversely, PLA2R1–sPLA2 binding has also been reported to mediate sPLA2 signaling by activating specific signaling pathways and/or by rerouting sPLA2 to specific intracellular compartments [19,22,30,47]. Physiologically, binding of certain sPLA2 and, in particular, PLA2G1B to PLA2R1 results in PLA2G1B mediating endotoxic shock [23] or a PLA2G1B protective effect against cardiac rupture after myocardial infarction [40].

In addition to sPLA2, collagens I and IV or integrin β1 can also bind PLA2R1. These bindings might impact migration and proliferation [2,40]. PLA2R1 can also bind mannose-coupled proteins but the role of this binding, shared with some receptors of the mannose receptor family, is currently unknown (Fig. 1) [44].

Until recently, there was a marked lack of reports looking at the intrinsic role of PLA2R1 to regulate various physiopathological states and, in particular, its role in cancer biology.

## 2. PLA2R1 promotes senescence in normal cells

Cells in senescence cease to proliferate (proliferation cannot be induced by mitogenic signals) and display several distinctive characteristics, such as activation of an immune response and major changes in their morphologies. This state is induced by various stresses, including, but not limited to, short telomeres, oxidative stresses or oncogenic stresses. Cellular senescence is thus a program activated in response to tumor-promoting stresses and aiming to block tumor initiation and progression in sensitive cells. Genetic events encouraging senescence escape are thus expected to promote cancer initiation and progression [8,13,21,27].

With the aim of identifying new tumor suppressive genes, we have performed a loss-of-function genetic screen to isolate genes which, when lost, allow the delay of, or escape from, replicative senescence. By this approach, we have isolated an shRNA directed against PLA2R1 which caused an extended life span in normal human fibroblasts. We then confirmed that a knockdown of PLA2R1 extends life span of normal human fibroblasts or epithelial cells [3]. Our data suggest a general impact on senescence as its knockdown decreases the sensitivity to oxidative stress-induced senescence [3] and permits escape from oncogenic stress-induced senescence *in vitro* [52]. The relevance of these *in vitro* observations is strongly supported *in vivo*, as PLA2R1 knockout mice are more sensitive to RAS-induced skin tumors by favoring oncogenic-stress induced senescence [52]. Concomitantly to these data obtained using loss of function tools, we observed that PLA2R1 constitutive expression in normal human cells induces a premature senescence [3,4]. *PLA2R1* is thus a new pro-senescing gene.

## 3. PLA2R1 promotes apoptosis and blocks transformation

All the data described above were generated in normal cells with functional tumor suppressive pathways, raising the questions of PLA2R1's effects, if any, on cancer cells. PLA2R1 constitutive expression in various cancer cell lines resulted in 2 distinct phenotypes.

First, its strong overexpression, achieved by strong selective pressure after transfection, resulted in cancer cell death in numerous cancer cell lines ([4] and unpublished data). Interestingly, and in the same settings, the overexpression of PLA2R1 pushes normal cells to senescence [4].

Second, overexpression of lower levels of PLA2R1, achieved by lowering the selective pressure after infection or by allowing the surviving cells in the first setting to grow, does not, or only moderately, impact cell death and cell proliferation. Nevertheless, in these settings, PLA2R1 expression blocks the ability of cancer cells to form colonies in soft agar whereas its knockdown promotes colony formation [52,53]. Xenograft experiments performed with human cancer cells knocked down for PLA2R1 or constitutively expressing PLA2R1 confirm these *in vitro* observations: PLA2R1 depletion accelerates cancer cell growth whereas PLA2R1 expression decreases cancer cell growth [53].

Thus, PLA2R1 promotes senescence in normal cells and induces cancer cell death or inhibits cell transformation. An important issue is to understand how this receptor might regulate these tumor suppressive pathways.

## 4. Downstream mediators of PLA2R1 tumor suppressive activity

While little is known about signaling pathways that might be regulated by PLA2R1, several reports propose that sPLA2 binding PLA2R1 activates a MAPK cascade [30,47]. Nevertheless, directly upregulating or downregulating PLA2R1, in experimental conditions in which it impacts senescence, does not modify phosphorylation levels of ERK1/2 and of p38 [3].

### *4.1. JAK2 activation*

To better understand PLA2R1 tumor suppressive activities, we screened for chemical inhibitors able to inhibit PLA2R1-induced cancer cell death. This strategy led to the isolation of a JAK2 specific inhibitor. We then confirmed by chemical and genetic tools, that JAK2 inhibition reversed PLA2R1-induced cell death or PLA2R1-induced transformation inhibition [52]. The JAK/STAT pathway is involved in senescence regulation, activated in response to numerous cytokines, which are known mediators of senescence [1,15,25,32]. In particular STAT5A, which can be activated by JAK2 [41], induced a premature senescence when constitutively activated [12,37]. In addition, JAK2 activation by the interferon gamma promotes cancer cell death and decreases proliferation, resulting in tumor growth inhibition [11,16]. Thus, JAK2 is a good PLA2R1 downstream tumor suppressive candidate. However, this model is complicated by the fact that JAK2 gain-of-function promotes tumor initiation and growth [5,7,24]. Together these results suggest that PLA2R1 is able, as is interferon, to orient the JAK/STAT pathway towards tumor suppressive activities, yet how this happens is unknown.

Molecularly, PLA2R1 and JAK2 can associate in the same complex and PLA2R1 induces JAK2 phosphorylation and subsequent STAT phosphorylation, increases the activity of a JAK/STAT reporter and increases JAK2/STAT target mRNA expression [52]. A PLA2R1 mutant lacking its intracellular domain, has the same effect as the full length PLA2R1, showing that PLA2R1 does not directly mediate an intracellular signaling [52] which is consistent with an interaction between the PLA2R1 extracellular domain and an unidentified receptor able to activate JAK2 (Fig. 2). Importantly, the Endo180 (also named MRC2) mannose receptor family member is able to act as such a co-receptor [18]. A challenging future issue is to identify the direct partner of PLA2R1 responsible for JAK2 activation.

### *4.2. Reactive oxygen species (ROS)*

Cell metabolism generates basal ROS production. ROS steady state levels can increase in response to various stresses, due to either an increase in production and/or a decrease of detoxifying systems. Increased ROS levels are a known inducer of cellular senescence and of cell death [36,45,50,51].

Normal cells constitutively expressing PLA2R1 display increased ROS production, leading to increased DNA damage and subsequent activation of the p53 pathway. The knockdown of PLA2R1 leads to the opposite events. Decreasing ROS levels by adding anti-oxidants is sufficient to overcome PLA2R1-induced senescence, demonstrating the important role of ROS [3] (Fig. 3).

Cancer cells constitutively expressing PLA2R1, also display increased ROS levels, and this increased ROS level leads to cancer cell death (Fig. 3). Chemical inhibition of various ROS-producing systems enabled the identification of a crucial role of the electron transport chain in this process. Indeed, inhibition of ETC complex I, III or V by, respectively, rotenone, antimycin A or oligomycin, reverses PLA2R1-induced ROS accumulation and cell death [4]. PLA2R1-induced cell death also occurs in cancer cells with nonfunctional p53, suggesting that p53 is one executor of PLA2R1 effects, among others, downstream of ROS. The molecular mechanism activated by PLA2R1 and leading to ROS generation, likely *via* the ETC, is still unknown. Nevertheless, we can speculate that JAK2 is involved in this process, but further work has to be done to confirm this and to identify the pathway downstream of JAK2 leading to ROS production.

## 5. PLA2R1 expression and regulation in cancer

Taking into account the strong tumor suppressive properties of PLA2R1, it is expected that its expression and/or its activity will decrease

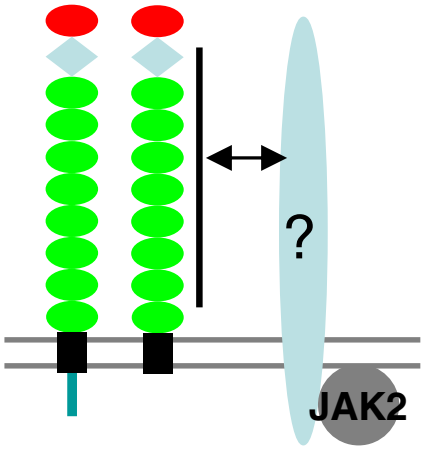


**Fig. 2.** PLA2R1 activates JAK2. PLA2R1 might interact through its extracellular domain to an unidentified receptor. This interaction should promote JAK2 activation and subsequent tumor suppressive pathways.

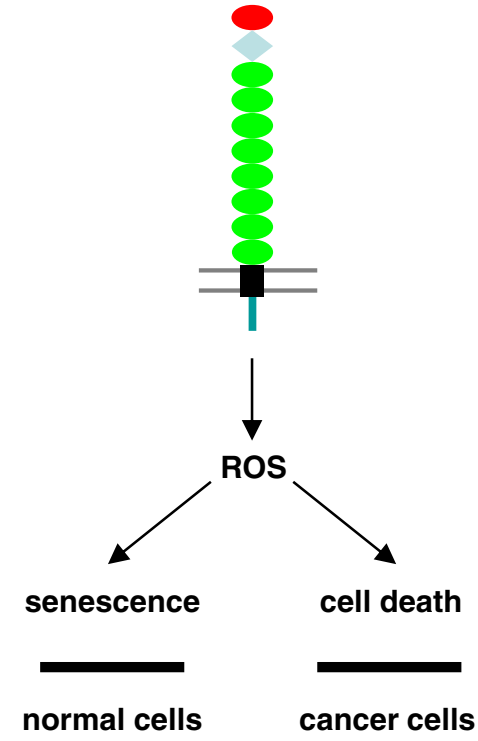


**Fig. 3.** PLA2R1 increases ROS production leading to senescence in normal cells or cell death in cancer cells.

in cancer cells. Analysis using the Oncomine microarray database (Compendia Bioscience, Ann Arbor, MI), allowed the examination of the variations of PLA2R1 mRNA levels in the main cancer types, demonstrating that PLA2R1 expression is lowered in most cancer types (except pancreatic and gastric cancers) (Table 1) [52]. This decrease in PLA2R1 levels is confirmed in breast [4] and kidney [53] cancers as well as in melanoma (unpublished data) by RTqPCR and/or by IHC (Table 1).

Interrogation of the COSMIC (Catalogue Of Somatic Mutations In Cancer) database shows that the Copy Number Variation of *PLA2R1* gene decreases only in breast cancers and is not decreased, and may even be increased, in other cancer types. PLA2R1 decreased expression in cancer cannot thus be explained by loss of the gene. Promoter hypermethylation in CpG rich islands is a classic way used by the cancer cells to decrease expression of tumor suppressors [26]. Interestingly, the *PLA2R1* transcription start site is indeed surrounded by CpG islands. Early experiments showed that the PLA2R1 promoter is hypermethylated in leukemia [39]. Another study from our team also concluded that the PLA2R1 promoter is hypermethylated in clear cell renal cell carcinoma (RCC)-derived cells in which PLA2R1 is not expressed. Induction of PLA2R1 promoter demethylation is sufficient to induce PLA2R1 expression [53].

RCC occurs because of Von Hippel–Lindau gene (VHL) loss of function [29]. Loss of the E3 ubiquitin ligase VHL in RCC results in increased HIFα stability. This stabilization of HIFα proteins, particularly HIF2α, is thought to be a driving force of RCC initiation and progression [38,46]. Furthermore, c-MYC, which is known to mediate HIF2α oncogenic effect [20], is known to mediate part of its activity by repressing the expression of known tumor suppressors such as p21 and p27 CKIs (Cyclin dependent Kinase Inhibitors) [20]. Repressive transcriptional activity of c-MYC is known to rely, at least in part, on the recruitment of DNMT (DNA Methyl Transferases) and thus induction of DNA methylation and transcriptional repression [10,31]. In RCC-derived cells, HIF2α, through c-MYC binding on PLA2R1 promoter, on the same regions as the methylated ones, favors PLA2R1 promoter methylation and its subsequent downregulation. This suggests that c-MYC mediates PLA2R1

**Table 1**
Summary of PLA2R1 expression in cancer. Cancer types displaying an increase or decrease of PLA2R1 (p value < 0.05, fold > 1.5 and 2 studies going in the same way) using microarray data (Oncomine database) were displayed. When available, confirmations of these microarray data at different levels (RNA by RTqPCR, proteins by IHC) are indicated. D means Decreased in cancer when compared to matched normal tissues, I means Increased, nd means not determined, and u.p. means unpublished data.

| Major cancer types | Bladder | Breast | Cervical | Colorectal | Esophageal | Gastric | Head and neck | Kidney | Melanoma | Pancreatic |
|---|---|---|---|---|---|---|---|---|---|---|
| Microarray data (Oncomine) | D | D | D | D | D | I | D | D | D | I |
| Cancer cell lines (RTqPCR) | nd | Confirmed [4] | nd | nd | nd | nd | nd | Confirmed [53] | nd | nd |
| Cancer tissues (RTqPCR) | nd | nd | nd | nd | nd | nd | nd | [53] | Confirmed (u.p. data) | Confirmed (u.p. data) |
| Cancer tissues (IHC) | nd | nd | nd | nd | nd | nd | nd | [53] | nd | nd |

promoter methylation [53]. This oncogenic pathway and, in particular, gain of c-MYC functions, occurs in numerous cancer types [9] so we can presume that this repressive pathway is largely conserved across various cancer cell types. For example, in breast cancers we also observed PLA2R1 promoter hypermethylation when PLA2R1 expression is lost (unpublished data). Besides the few documented ways by which cancer cells downregulate PLA2R1 expression, it is probable that several other pathways contribute to this downregulation.

## 6. Future directions

The aim of this review, focused on the role of PLA2R1 in cancer biology, is to illustrate recent discoveries of this gene function. Since being cloned in the nineties, this gene was quite exclusively viewed, at least up to recently, as a modulator of certain sPLA2 effects, and thus attracted the interest only of the sPLA2 community [42,43]. In addition, the historical lack of experimental tools (for manipulation as well as detection) available as well as its generally low expression levels were additional obstacles preventing it from attracting the interest of a broader community. The situation has been changing since 2009 and major discoveries have been made: PLA2R1 was identified as a major antigen in idiopathic membranous nephropathy [6], a discovery not explored in this review focusing on cancer; it was isolated as a functional modulator of cellular senescence [3] that formed the starting point for most of the papers related to PLA2R1 and cancer, and those studied in this review.

Numerous unsolved problems should be tackled in the next few years such as its manipulation in mice cancer genetic models to evaluate its putative tumor suppressive role, isolation of its partner at the membrane that activates JAK2, describing the signaling pathways it regulates in depth, and understanding its impact on mitochondrial physiology among others. An important future issue is to determine the role of the sPLA2 that binds PLA2R1 on PLA2R1 tumor suppressive roles. Evidence suggests that, even if some sPLA2 and PLA2R1 regulate common processes such as senescence [28], the sPLA2 is not required for the PLA2R1 tumor suppressive effects. This has been suggested by using various PLA2R1 mutants and various sPLA2 inhibitors [4] but does not exclude that the sPLA2 can modulate the PLA2R1 activities. Beyond the sPLA2, a general question is how this receptor activity is regulated at various levels; binding of proteins, collagen, sugars, post-translational modifications and so on.

At this stage, we are convinced that *PLA2R1* is an important tumor suppressive gene and that the increasing knowledge of PLA2R1 functions in cancer will be of interest for the cancer biology community.

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