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Mini-review

Secreted phospholipases A_2 in cancer: Diverse mechanisms of action

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ABSTRACT

Secreted phospholipases A_2 (sPLA$_2$s) hydrolyse cell and lipoprotein phospholipid membranes to release free fatty acids and lysophospholipids, and can also bind to specific proteins. Several sPLA$_2$s have been associated with various cancers, including prostate, colon, gastric, lung and breast cancers, yet, their role is controversial and seems to be dependent on the cancer type, the local microenvironment and the enzyme studied. There is strong evidence that the expression of some sPLA$_2$s, most notably the group IIA, III and X enzymes, is dysregulated in various malignant tissues, where, as described in a number of *in vitro* and *in vivo* studies using mouse models and according to correlations between sPLA$_2$ expression and patient survival, a particular enzyme may exert either a pro- or an anti-tumourigenic role. It is becoming clear that there are multiple, context-dependent mechanisms of action of sPLA$_2$s in different cancers. First, the role of sPLA$_2$s in cancer has traditionally been associated with their enzymatic activity and ability to participate in the release of potent biologically active lipid mediators, in particular arachidonic acid-derived eicosanoids, which promote tumourigenesis by stimulating cell proliferation and cell survival, by abrogating apoptosis and by increasing local inflammation and angiogenesis. Second, several biological effects of sPLA$_2$s were found to be independent of sPLA$_2$ enzymatic activity, arguing for a receptor-mediated mechanism of action. Finally, recent studies have implicated sPLA$_2$s in the regulation of basal lipid metabolism, opening a new window to the understanding of the diverse roles of sPLA$_2$s in cancer. In this short review, we highlight the newest findings on the biological roles of sPLA$_2$s in cancer, with emphasis on their diverse mechanisms of action.

1. Secreted phospholipases A_2 (sPLA$_2$s)

Secreted phospholipases A_2 (sPLA$_2$s)[1] are lipolytic enzymes that act on membrane glycerophospholipids to release free fatty acids (FAs) and lysophospholipids by catalysing the hydrolysis of their *sn*-2 ester bond [1–3]. These low molecular mass, disulphide-rich and Ca^{2+}-dependent enzymes are secreted from a variety of cells and act in autocrine or paracrine manner on cell membranes and other extracellular phospholipid substrates, such as lipoproteins and microvesicles, as well as bacterial and viral membranes [2]. There are eleven sPLA$_2$ genes in humans and twelve in mice, encoding nine and ten active enzymes, respectively, and two sPLA$_2$-like proteins. They display different tissue and cell expression patterns and differ significantly in their structure, which in turn affects their secretion, enzymatic activity and ability to bind to several known receptors [1–4]. They also display specific enzymatic preferences for binding to and hydrolysis of different types of phospholipids, with some enzymes showing a net preference for anionic or zwitterionic phospholipid substrates and

Abbreviations: AA, arachidonic acid; ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; cPLA$_2\alpha$, cytosolic group IVA phospholipase A_2; CPT1, carnitine palmitoyltransferase 1; EGFR, epidermal growth factor receptor; FA, fatty acid; ERK, extracellular signal-regulated kinase; FAS, fatty acid synthase; LD, lipid droplet; LPC, lysophosphatidylcholine; MAPK, mitogen-activated protein kinase; sPLA$_2$, secreted phospholipase A_2; PG, prostaglandin; PGE2, prostaglandin E2; PLA2R1, M-type receptor for secreted phospholipases A_2; PUFA, polyunsaturated fatty acid; SCD-1, stearoyl-CoA desaturase-1; SREBP-1, sterol regulatory element-binding protein; TAG, triacylglycerol.

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[1] sPLA$_2$ enzymes are abbreviated with a lowercase letter indicating the species of origin (h, human; m, mouse) and with uppercase letters and Roman numerals denoting the sPLA$_2$ group (GIB, GIIA, GIII, GX and GXIIB).

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some being almost devoid of enzymatic activity [1,5], suggesting distinct and non-redundant biological roles for each $sPLA_2$ [5]. The cellular effects of $sPLA_2$s have most commonly been associated with the release of arachidonic acid (AA) and its eicosanoid metabolites, as well as signalling triggered by binding to specific receptors [1–3,6–8]. However, $sPLA_2$ activity also leads to the release of a mixture of other bioactive lipids, such as mono- and polyunsaturated FAs (PUFAs), including omega-3 PUFAs, and lysophospholipids, such as lysophosphatidylcholine (LPC). Many, if not all, of these lipids have various signalling roles, act as biosynthetic precursors or have direct metabolic roles. Collectively, the multitude of phospholipid substrates, the primary and secondary lipid products of $sPLA_2$ activity and the various known cellular effects of $sPLA_2$s provide a rationale for their involvement in a variety of physiological processes and diseases, including lipid digestion and remodelling, acute and chronic inflammatory diseases, cardiovascular diseases, reproduction, host defence against infections and cancer [2,3].

2. Expression and functional role of $sPLA_2$s in cancer

Aberrant expression of various human $sPLA_2$s in tumours and cancer cells has been associated with the pathology of several types of malignancies, including, but not limited to, cancers of the colon, breast, stomach, oesophagus, ovaries and prostate (for a concise review see Ref. [9]), but the functional roles of $sPLA_2$s are incompletely understood and seem to be dependent on the enzyme studied, the tissue and cancer type involved (Table 1). It must be noted that the majority of mechanistic and functional reports to date rely on *in vitro* cell culture and basic *in vivo* mouse model studies, and that a clear and unequivocal role in the development or progression of cancer has not been proven for any of the $sPLA_2$ enzymes. Among $sPLA_2$s, the group IIA (GIIA) and X (GX) enzymes are widely expressed in different tissues, are highly enzymatically active [1–3,5], and are also the most studied $sPLA_2$s in cancer so far. It should thus not be surprising to the reader that the apparent focus of this mini-review is on these two enzymes, although every effort was made to include all relevant existing reports on the emerging role of other members of the $sPLA_2$ family in cancer as well.

The expression of the human group IIA (hGIIA) $sPLA_2$ is high in prostate [10,11], oesophageal [12] and lung [13] cancer cells *in vitro*. In mouse xenograft models, inhibition of hGIIA $sPLA_2$ in prostate [10] and lung [14] cancer cells, when implanted into nude mice, results in smaller tumours. In humans, the expression of hGIIA $sPLA_2$ is increased in the serum or tumours of patients with prostate [10,11,15–17], oesophageal [18] and lung cancer [13,18,19], and importantly, it is associated with poorer patient survival in prostate [15] and lung cancer [19]. Of interest, recent *in vitro* results suggest that the lung cancer phenotype is supported by hGIIA $sPLA_2$, which was found to be overexpressed in lung cancer stem cells relative to their non-stem cell counterparts [20]. The elevated levels of hGIIA in the plasma of lung and prostate cancer patients [11,19] have led to suggestions of a potential biomarker role for the enzyme. However, at least in the case of prostate cancer, the presence of high concentrations of hGIIA in serum may not reflect neoplastic transformation, but rather inflammation, characteristic also of benign prostate hyperplasia [16,17]. Based on the above findings, a pro-tumourigenic role of the enzyme has been suggested in prostate, oesophageal and lung cancer. No data is available on the role of other $sPLA_2$s in these cancers.

On the contrary, the increased expression of hGIIA $sPLA_2$ in gastric cancer cell lines and in tumours of patients with gastric cancer appears to be associated with an anti-tumourigenic role of the enzyme, as it reduces cell migration and invasiveness *in vitro*, its expression correlates with longer survival and is a predictor of a

Table 1
Functional role of $sPLA_2$s in cancer. Studies in which the mechanisms of action or functional roles of $sPLA_2$s were not assessed were mostly omitted from this table. Please refer to Ref. [9] for a thorough summary of such studies published before 2010 and to the text for studies published after 2010.

Cancer	$sPLA_2$ enzyme	Role	Expression *in vitro*	Expression in patients (serum and/or tumours)	Effects *in vitro*	Effects *in vivo*	Association with clinicopathological features and survival	References
Breast	GIIA	Pro-tumourigenic	High in HER2-positive cells	Increased	ND	ND	Shorter patient survival	[53–55,57]
	GX	Pro-tumourigenic	High in luminal-like, low in basal-like cells	Increased in invasive and luminal tumours	Increased cell proliferation; resistance to apoptosis	ND	ND	[57,58]
Colon	GIIA	Pro- and/or anti-tumourigenic	Increased	Increased	Increased cell proliferation	Suppression of tumourigenesis; increased xenograft tumour size	ND	[25–32,44,46]
	GIII	Pro-tumourigenic	ND	Increased	Increased cell proliferation	Increased xenograft tumour size	Genetic variant is associated with higher risk of cancer	[27,47,48]
	GX	Pro- and/or anti-tumourigenic	ND	Increased	Increased cell proliferation	ND	Longer patient survival; less frequent metastasis	[27,46,49–51]
Gastric	GIIA	Anti-tumourigenic	Increased	Increased in early-, decreased in late-stage tumours	Reduction of cell migration and invasiveness	ND	Longer patient survival; less frequent metastasis	[21–24]
Lung	GIIA	Pro-tumourigenic	Increased	Increased	Increased cell proliferation; lower apoptosis	Knockdown of GIIA results in slower growth of xenograft tumours in mice	Shorter patient survival	[13,14,18,19]
Oesophageal	GIIA	Pro-tumourigenic	Increased	Increased	Increased cell proliferation	ND	ND	[12,18]
Prostate	GIIA	Pro-tumourigenic	Increased	Increased	Increased cell proliferation	Inhibition of GIIA results in slower growth of xenograft tumours in mice	Shorter patient survival	[10,11,15–17]

ND, not determined or not reported.