

## Review Article

# The Role of the Secretory Group IIa Phospholipase A2 (sPLA2-IIa) in Ocular Surface Inflammation

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**Abstract**

Recent progress implies that sPLA2-IIa plays a critical role in dry eye disease (DED) associated ocular surface inflammation beyond its well-known bactericidal. Understanding of the mechanisms and pathophysiology of this enzyme may provide the key leading to the cure of DED. This article is aimed to review the functions of sPLA2-IIa and the role it plays in DED.

Millions of people suffer from ocular surface inflammation such as dry eye disease (DED), especially adult women above the age of 50 [1]. Although the pathogenesis of DED is still not clearly known, research has shown that sPLA2-IIa and various other inflammatory mediators may be useful as important biomarkers in ocular surface inflammation [1-3].

The enzymes in group two Phospholipase A (PLA2) catalyze the hydrolysis of membrane glycerophospholipids at the *sn*-2 position to yield lysophospholipids and free fatty acids including arachidonic acid (AA), which is the precursor of many inflammatory mediators such as prostaglandin E2 (PGE2), leukotrienes and other eicosanoids [2]. To date, more than 30 PLA2 enzymes are identified in mammals which have been subdivided into six major families: secreted PLA2 (sPLA2), Ca<sup>2+</sup>-dependent cytosolic PLA2 (cPLA2), Ca<sup>2+</sup>-independent PLA2 (iPLA2), platelet-activating factor acetylhydrolase (PAF-AH), lysosomal PLA2 (LPLA2), and adipose-specific PLA2 (AdPLA2) [4]. Humans and rodents share at least 11 isoforms of sPLA2, of which sPLA2-IIa, sPLA2-V and sPLA2-X are found to be associated with ocular inflammatory responses [5]. Among the three, the most intensively studied is sPLA2-IIa due to its linkage to numerous inflammatory diseases such as rheumatoid arthritis (RA), [6] atherosclerosis, [7] septic shock, [8] inflammatory bowel disease [9] and asthma [10].

The ocular surface system consists of the cornea (CN), conjunctiva (CNJ), lacrimal glands (LG), tarsal glands, nasolacrimal duct, and their associated tear and connective tissue matrices, as well as the eyelids and eyelashes [1]. sPLA2-IIa is a known innate barrier on the ocular surface against bacterial infection [3]. The

sPLA2-IIa enzyme causes the instability of tear film [11,12]. Disturbance of the homeostatic balance of ocular surface system can result in osmotic, mechanical and inflammatory damage [1]. When the ocular surface is compromised, intracellular signaling pathways are activated to produce cytokines, chemokines and other proinflammatory mediators, which recruit leukocytes from lymphoid tissues to the inflammatory sites. It has been suggested that T-cell-mediated immunity plays a central role in DED via T<sub>H</sub>1 and T<sub>H</sub>17 cell activities [1,13]. Cytokines released by these effector T cells promote the production of inflammatory mediators and facilitate the migration of more pathogenic immune cells, leading to severe ocular surface inflammation [1]. Beside these general immune responses, studies have demonstrated a significantly elevated level of sPLA2-IIa and its enzymatic activity in ocular surface inflammatory diseases, including chronic dry eye disease (DED), [2,3,5] allergic conjunctivitis (AC), [11] and contact lens intolerance [12].

In our research, DED is used as a disease model of ocular surface inflammation. Ocular surface samples from patients with DED and from BALB/c mice with induced DED have been established to study the pathogenesis of DED and signaling pathways in which sPLA2 serves as an inflammatory mediator. BALB/c strain mice have a functional *PLA2G2A* gene, and DED was induced via scopolamine injection with air ventilation. Phenol-red thread test, PAS-HE staining, and CN fluorescence staining confirmed the presence of an inflammatory reaction. Each procedure demonstrated typical characteristics of DED including a significant reduction in tear production, lower density of goblet cells, and heavier CN staining with a typically punctuated pattern. Collective results from our lab have shown:

(1) tears of DED patients have an increased sPLA2-IIa expression and enzymatic activity along with the increase of various inflammatory cytokines compared to that of normal tears; (2) the increased sPLA2-IIa activity in DED tears of inflamed ocular surface results from the upregulation of the *PLA2G2A* gene in the CNJ epithelia; (3) sPLA2-IIa is mainly expressed in the CNJ epithelia rather than the CN epithelia, which confirms the results from immunofluorescence staining of sPLA2-IIa. Tear cytokine quantification concluded a correlation between an increase in sPLA2 expression and an increase in inflammatory cytokines and chemokines, such as IL-1 $\beta$ , IL-6, IFN- $\gamma$  and TNF- $\alpha$ . Further experimentations revealed that sPLA2-IIa significantly amplifies PGE2 production in CNJ organ cultures from either DE models or normal cells pretreated with proinflammatory cytokines TNF- $\alpha$  or IL-1 $\beta$ . This indicates the role of sPLA2-IIa in synergistically amplifying ocular surface inflammation with other cytokines, chemokines and inflammatory mediators. However, upon the addition of sPLA2-IIa specific inhibitors like S-3319, this amplification was reduced in a dose-dependent manner. All these results indicate that sPLA2-IIa plays a pivotal role as an inflammatory mediator when the ocular surface is compromised and may have the potential for becoming a good target for DED treatment [2,3,5].

sPLA2-IIa has been found to be associated with a diverse number of inflammatory diseases including DED, that negatively impact people's lives. Future studies of sPLA2-IIa and related inflammatory cytokines, chemokines and mediators will provide a better understanding in using them as noninvasive biomarkers to diagnose the manifestation and severity of DED. Confirming the role of sPLA2 in the ocular surface inflammation is important for improving our understanding of DED pathogenesis and inflammatory response mechanisms, including the amplification of ocular surface inflammation. In the future, sPLA2 may serve as a vital target for treatment of DED and possibly other related inflammatory diseases via specifically designed sPLA2 isoform inhibitors.

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