Phospholipase A_2s are enzymes which share as their common characteristic the capacity to hydrolyze fatty acids from the *sn*-2 position of glycerophospholipids (for review see reference 1). Group I and group II phospholipase A_2 are two sets of enzymes in a highly conserved family of secreted or extracellular phospholipase A_2 ($sPLA_2$) found in mammals. This family of $sPLA_2$ has a number of features which distinguish it from the other major phospholipase A_2 families such as group IV (cytolsolic) PLA_2. These features include a relatively low molecular weight (14–16 kD), high disulfide bond content and a requirement for relatively high concentrations of Ca^{2+} for catalysis. $sPLA_2$ have been studied extensively in mammals and snake venoms for the past six decades, yet little is currently known about the physiological and pathophysiological roles of these enzymes. Inspection of the many papers published in the last few years reveals that these $sPLA_2$'s have the potential to mediate a wide range of biological activities including: (*a*) potent antibacterial effects; (*b*) a key component in the digestion of glycerophospholipids; (*c*) enzymatic producers of lyso-phospholipids that contribute to electrophysiologic alterations that lead to arrhythmogenesis in the heart or alter airway permeability and surfactant properties in the lung; (*d*) serum markers and potential regulators of severe illnesses such as sepsis, shock, organ injury, and pancreatitis, all of which are linked to the development of adult respiratory distress syndrome and multiple organ failure; (*e*) regulators of platelet aggregation and hemorrhagic diseases; (*f*) pro-inflammatory components in diseases such as rheumatoid arthritis and asthma; and (*g*) initiators of cell proliferation in several cancer cell lines and a potent modifying locus of intestinal tumorigenesis in mice.

This daunting list of activities and diseases raises fundamental questions as to whether $sPLA_2$ causes or is merely associated with many of the aforementioned effects. Perhaps the only place where $sPLA_2$ unambiguously has been demonstrated to regulate an in vivo process is digestion of glycerophospholipids in the intestine. However, even in this case, it is unlikely that the gut is the only site of action for group I $sPLA_2$ since large quantities of message and protein levels are found in other tissues including the lung and spleen. Group II $sPLA_2$ is also found in many cells and tissues including platelets, mast cells, neutrophils, vascular smooth muscle cells, liver, spleen, placenta, cartilage, and intestinal mucosa. Therefore, the somewhat ubiquitous distribution of group I and group II among mammalian cells and tissues also provides few hints as to the major physiological and pathophysiological roles of these enzymes.

With the backdrop of so many potential biological activities and potential sources for both group I and group II $sPLA_2$, new specific inhibitors or models are critically needed to better define the essential processes induced by $sPLA_2$ activation. While some inhibitors have been developed which block PLA_2 activity and inflammatory processes in in vivo models of disease, the lack of selectivity of most of these inhibitors against group I, group II and cytosolic PLA_2 make interpretation of such studies equivocal. Very recently, genetic models have been developed to address the complex issue of the role of $sPLA_2$ isotypes. In this issue of *The Journal*, Grass and colleagues (2) describe an elegant group of experiments where they generate transgenic mice expressing high (eightfold higher than nontransgenic litter mates) quantities of group II PLA_2 in a variety of tissues including liver, lung, kidney, and skin. They then used this model to examine the pathological events predominantly in the skin associated with such overexpression. Histopathological analysis of these animals revealed a disorder of the skin consisting of hyperkeratosis, epidermal hyperplasia, and adnexal hyperplasia. The chronic, epidermal hyperplasia and hyperkeratosis observed in these mice is similar to that seen in a variety of skin disorders including human psoriasis. However, in contrast to psoriasis, these animals had no increase in inflammatory cell influx into the skin. Interestingly, skin graft experiments in this study revealed that overexpression of group II PLA_2 in the skin, and not elevated levels in the serum was responsible for the phenotypic abnormalities. Two other groups have examined the intradermal injection of $sPLA_2$ in rabbit and swine skin (3, 4). The reactions to the $sPLA_2$ injections were characterized by transient erythema as well as microscopic changes such as cell infiltration and epidermal hyperplasia. An inhibitor, BMS 181162, developed against group II PLA_2 blocked both the inflammation and the epidermal hyperplasia during TPA induced skin injury in mice. Taken together, these studies suggest that high levels of $sPLA_2$ in the skin induce marked changes in skin phenotype as indicated by the observed epidermal hyperplasia. The fact that Grass and colleagues find the hyperplasia in the absence of inflammation suggests that these may be independent events seen during psoriasis. For example, it may be that concentrations of group II PLA_2 generated in the skin of the transgenic mice are high enough to induce keratinocyte proliferation but not high enough to cause edema with concomitant influx of inflammatory cells. In contrast, intradermal injections may achieve localized group II PLA_2 levels sufficiently high enough to cause both epidermal hyperplasia and inflammation.

The mechanisms by which group II PLA_2 induces either an inflammatory response or epidermal hyperplasia are largely speculative at this time. In the case of epidermal hyperplasia, it is interesting to note that $sPLA_2$ induces proliferation of several transformed cell lines and has been proposed as an enhancing factor for epidermal growth factor binding to cells. In addition, arachidonic acid or its oxygenated products have been proposed to mediate several pivotal downstream events associated with cell proliferation including the regulation of PKC and MAP kinase. Alternatively, $sPLA_2$ may bind to specific membrane receptors and directly trigger key biological events necessary for proliferation (for review see reference 5). In this regard, it is interesting to note that intradermal injection of inactivated $sPLA_2$ (no hydrolytic activity) causes similar phenotypic changes in skin to those observed with injection of fully active $sPLA_2$.

J. Clin. Invest.

0021-9738/96/05/2161/02 $2.00
Volume 97, Number 10, May 1996, 2161–2162

As enumerated earlier, $sPLA_2$ is likely to have a central role in regulating many disease processes. However, discerning where it induces, rather than is merely associated with, a biological event is a central challenge for those of us interested in this family of enzymes. Models such as the one described in this issue of *The Journal* provide us with a new tool to approach this fundamental and consequential question.

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