

Group X secreted Phospholipase A2, atherosclerosis and beyond.

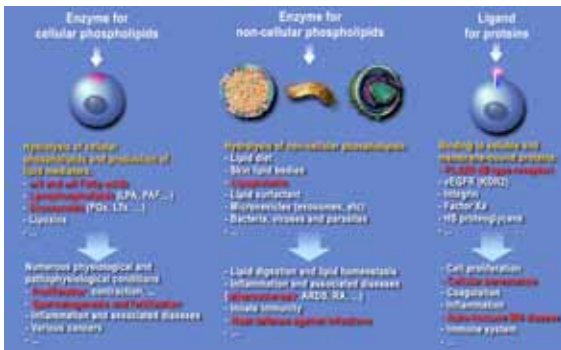
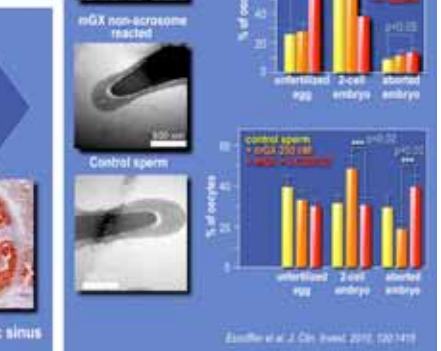
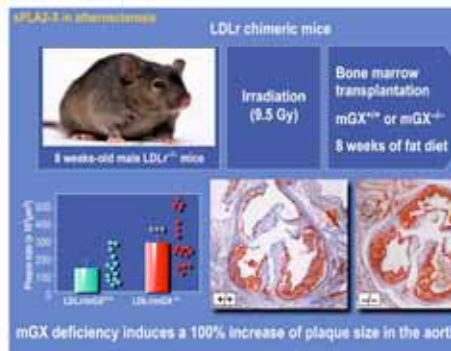
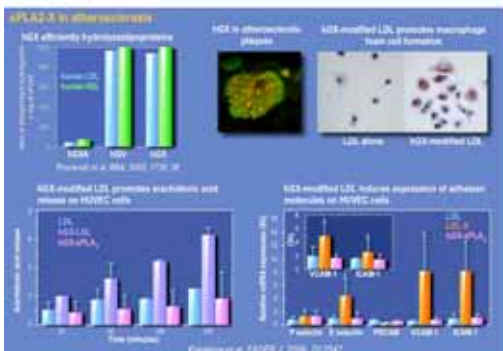
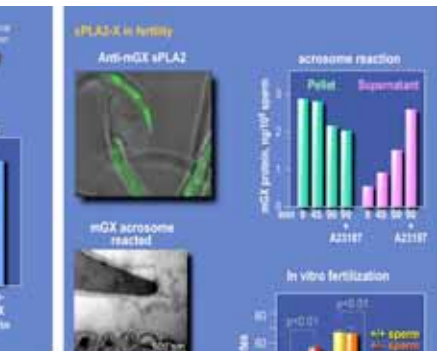
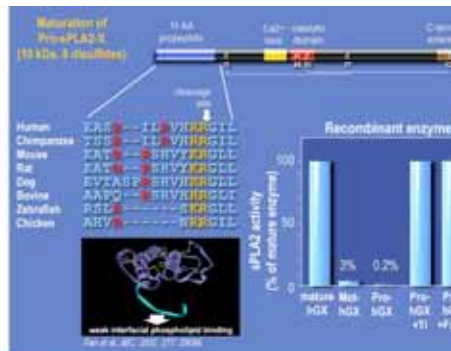
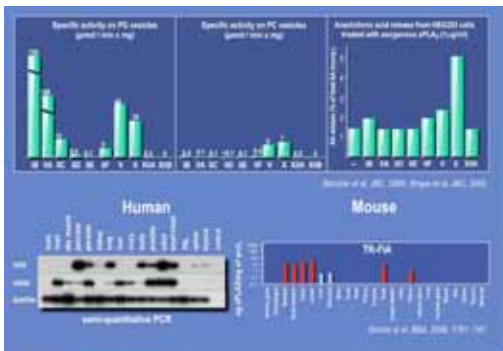
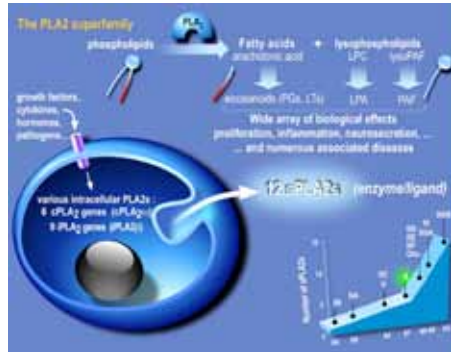


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Synopsis of the ANR project

The ANR Physio2006 project « sPLA2/atherosclerosis » was coordinated by Dr Gérard Lambeau, a world expert on sPLA2s. The project associated the laboratories of Ziad Mallat (HEGP, Paris), Ewa Ninio (INSERM UMR937, Paris) and Tabassome Simon (APHP, Paris), 3 laboratories with a long-lasting expertise in atherosclerosis. The project started on 2007 and was supported by ANR for a total budget of 240,000 € with a total cost of about 540,000 €.

The major aim was to study the specific role of group X secreted phospholipase A2 (sPLA2-X) in atherosclerosis, a chronic inflammatory disease of the arterial wall. Several sPLA2s are likely to play key roles in this disease by i) promoting the formation of pro-atherogenic lipoproteins, ii) producing lipid mediators, and iii) activating immune cells within the atherosclerotic plaque. We focused on sPLA2-X because of its high expression in immune cells and high catalytic activity on phosphatidylcholine from cells and lipoproteins. Our objectives were to analyze: i) the expression of sPLA2-X and its activation during secretion, ii) its *in vivo* role in mouse models of atherosclerosis and iii) its possible use as a novel biomarker of cardiovascular secondary prevention in a large cohort of patients with acute myocardial infarction.



Major results and future directions

Our major results have shown that sPLA2-X is 1) activated by proprotein convertases during secretion, 2) is present in mouse and human atherosclerotic plaques, 3) has a novel protective role in the Ldlr KO mouse model of atherosclerosis, 4) might be a novel biomarker for cardiovascular diseases. The role of sPLA2-X is contrasting with that of sPLA2-IIA, -V and -III that are pro-atherogenic in several mouse models of atherosclerosis including Ldlr. Our results further support the notion that sPLA2s are likely key effectors and biomarkers in atherosclerosis. They also highlight opposite roles of distinct sPLA2 isoforms and suggest that: i) the current clinical trials using pan sPLA2 inhibitors may failed as it is likely necessary to very specifically inhibit (sPLA2-IIA, -V or -III) or activate (sPLA2-X) them to control atherosclerosis progression, and ii) it will be important to determine the serum concentration of each sPLA2 isoforms to possibly use them as biomarkers of cardiovascular diseases.

Beyond atherosclerosis, and thanks to the ANR program, we have also identified novel possible roles of sPLA2-X in colon cancer (Surrel et al. (2009) Mol. Pharmacol. 76, 778-790), male fertility (Escoffier et al. (2010) J. Clin. Invest. 120, 1415-1428) and host defense (Guillaume et al. JBC, in revision).

Scientific production, patents and new contracts generated by the sPLA2/atherosclerosis program

1. Rouault et al. (2007) Biochemistry 46, 1647-1662.
2. Gora et al. (2009) J. Mol. Med. 87, 723-733.
3. Gora, et al. (2010) Faseb J. 24, 3284-3297.
4. Alt-Oufella et al. (2011) Submitted to Circulation.
5. Jemel et al. (2011) submitted to JBC.
6. Lambeau & Gelb (2008) Review, Annu. Rev. Biochem. 77, 495-520.
7. Murakami et al. (2010) Review, Biochimie, 92, 561-582.
8. Karabina et al. (2010) Review, Biochimie 92, 594-600.
9. Mallat et al. (2010) Review, Circulation, 122, 2183-2200.
10. 2 Patents: Group X sPLA2 for use in the treatment of atherosclerosis. EP09306064 filed on November 6, 2009, extension PCT/EP2010/068864 filed on November 5, 2010. Use of sPLA2-V and/or sPLA2-X as cardiovascular risk factors. Provisional US patent N°61/172,005 filed April 23, 2009.
11. Contracts and MTA with two private companies, CNRS-JSPS collaboration with Dr Murakami (University of Tokyo).

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