Inserm
Délégation régionale
Midi-Pyrénées, Limousin

UMR 1048 (I2MC)
Equipe 10

Anne Nègre-Salvayre
Lipides, peroxydation, signalisation et pathologies vasculaires

Inserm U 1048 - I2MC
CHU de Rangueil
1, avenue Jean Poulhès - BP 84225
31432 Toulouse cedex 4 - France
Tel : 05.61.32.20.59
Fax : 05.61.32.20.84
E-Mail : anne.negre-salvayre@inserm.fr

Cette équipe de recherche fait partie de l'unité Inserm 1048, mixte avec l'université Paul Sabatier (I2MC ou Institut des maladies métaboliques et cardiovasculaires).

Objectif scientifique

La modification des LDL joue un rôle essentiel dans l'athérogenèse c'est à dire les premières étapes de la formation des lésions, telles que l'accumulation des cellules spumeuses, et la réponse immunitaire pro-inflammatoire. Par ailleurs, les lipides oxydés s'accumulent dans les lésions d'athérosclérose, en particulier dans le core nécrotico-lipidique. Ils amplifient localement la réponse inflammatoire, stimulent la migration et la prolifération des cellules musculaires lisses, génèrent une dysfonction des voies de survie et la survenue d'évènements apoptotiques, et pourraient donc contribuer in situ à la fragilisation des la plaque. Notre projet a pour objectif d'étudier l'implication des lipides oxydés (oxystérols, phospholipides oxydés, aldéhydes), dans le développement des lésions avancées, leur implication dans la néovascularisation des plaques, ou dans l'apoptose et la déstabilisation des lésions. Nous étudions par ailleurs les mécanismes de défences activés par les cellules vasculaires (stress du réticulum endoplasmique, autophagie, mitophagie) dont les fonctions pourraient être progressivement inhibées par les effets délétères des lipides oxydés, les liens de ces lipides avec les voies de signalisation ambivalentes telles que la voie des sphingolipides (céramide apoptotique vs sphingosine 1-phosphate mitogène et impliquée dans la survie).
L'activité clinique de l'équipe s'intéresse à des techniques innovantes d'imagerie médicale vasculaire computationnelle (CFD), et des projets translationnels avec le Service de Cardiologie du CHU Rangueil, Toulouse, sur la caractérisation des propriétés et la régulation épigénétique des HDL chez les patients coronariens.

Retombées attendues en santé

- Meilleure comprehension des mécanismes moléculaires et cellulaires impliqués dans la formation et l'évolution des plaques d'athérosclérose, ou les mécanismes du rejet chronique de greffe
- Nouvelles approches thérapeutiques anti-athérogénes, anti rejet de greffe

Mots clés

Athérosclérose, artériosclérose de greffe, marqueurs, stabilité, instabilité, angiogenèse, mitophagie, autophagie, inflammation, apoptose, prolifération, transduction du signal, dysfonction endothéliale, imagerie.

Formation à la recherche

- Masters 1 et 2
- Stages Erasmus
- Thèses
- Stages de formation BTS
- Thèses d'exercice Pharmacie, Médecine

Coopérations / Partenariats

Nombreuses collaborations en France, en Europe, aux Etats-Unis et au Japon:
- Hannun,Y., Medical University of South Carolina, Department of Biochemistry and Molecular Biology, Charleston, South Carolina;
- Uchida K., Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo 113-8657, Japan.
- Martinet W., Antwerp University
- Zarkovic N, LAbOS, University of Zagreb, Croatia
- Rouis M, UMR 8256 - Biological Adaptation and Ageing, UPMC Paris

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Partenariats avec l'Université,le CNRS, et contrats privés

Principales publications du laboratoire

- Galvani S et al: A key role for MMPs and neutral sphingomyelinase-2 in transplant vasculopathy triggered by anti-HLA antibody. Circulation 2011, 124:2725
- Muller C, et al: HDLs inhibit endoplasmic RE and autophagic response induced by oxidized LDL. Cell Death Differ 2011, 18:817
- Larroque-Cardoso P, et al: Role of protein kinase C delta in ER stress and apoptosis induced by oxidized LDL in human vascular SMC Cell Death Dis 2013, 4:e520.
- Muller C, et al: HDLs inhibit endoplasmic RE and autophagic response induced by oxidized LDL. Cell Death Differ 2011, 18:817
- Larroque-Cardoso P,et al. Elastin Modification by 4-Hydroxynonenal in Hairless Mice Exposed to UV-A. Role in Photoaging and Actinic Elastosis. J Invest Dermatol. 2015;135(7):1873
- Cinq-Frais C, et al: Annexin II-dependent actin remodelling evoked by hydrogen peroxide requires the MMP/sphingolipid pathway. Redox Biol 2015,4:169
- Trayssac M, et al: Role of S1P in Transplant Vasculopathy Evoked by Anti-HLA Antibody. Am J Transplant 2015, 15:2050
- Camare C, et al: The neutral sphingomyelinase-2 is involved in angiogenic signaling triggered by oxidized LDL. Free Radic Biol Med 2016, 93:204
- Swiader A, et al: Mitophagy acts as a safeguard mechanism against human vascular smooth muscle cell apoptosis induced by atherogenic lipids. Oncotarget 2016, 7: 28821

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Regional Authority
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Team 10

Anne Nègre-Salvayre
Lipid peroxidation, Signaling and Vascular Diseases

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Inserm Team working in the Unit 1048, in association with Paul Sabatier University (I2MC, The Institute of cardiovascular and metabolic diseases).

Scientific objective

LDL modification plays an essential role in atherogenesis, i.e. the early stages of lesion formation, characterized by the accumulation of foam cells, and pro-inflammatory immune responses. Oxidized lipids accumulate in the atherosclerotic lesions, in particular in the necrotico-lipid core. They amplify locally the inflammatory response, stimulate the migration and proliferation of smooth muscle cells, generate a dysfunction of survival pathways and the occurrence of apoptotic events, thus could contribute in situ to plaque fragilization and rupture. Our aim is to study the involvement of oxidized lipids (oxysterols, oxidized phospholipids, aldehydes) in the development of advanced lesions, their role in plaque neovascularization and destabilization. Our aim is to investigate and clarify the defense mechanisms activated by vascular cells (endoplasmic reticulum stress, autophagy, mitophagy), whose function could be progressively inhibited by the deleterious effects of oxidized lipids, the links of these lipids with Janus-faced signaling pathways evoked by sphingolipid mediators (apoptotic ceramide vs mitogenic sphingosine 1-phosphate).
The clinical activity of the team focuses on innovative techniques of computational vascular medical imaging (CFD) and translational projects with the Cardiology Department of the Rangueil Hospital in Toulouse, on the characterization of HDL properties and their epigenetic regulation in coronary patients.

Expected health effects

We aim to
- Better understand the physiopathological mechanisms involved in the development and evolution of the atherosclerotic lesion, and in graft rejection
- Develop new therapeutical approaches efficient against atherosclerosis and graft rejection

Key words

Atherosclerosis, graft arteriosclerosis, markers, stability, unstability, angiogenesis, autophagy, mitophagy, inflammation, apoptosis, proliferation, signal transduction, endothelial dysfunction, plaque imaging.

Research training

- Masters
- Erasmus stays
- PhD thesis
- Polytechnic stays (for technicians)

Cooperation and Partnerships

A number of collaboration with french groups as well as groups in Europa America and japan.
- Hannun,Y., Medical University of South Carolina, Department of Biochemistry and Molecular Biology, Charleston, South Carolina;
- Uchida K., Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo 113-8657, Japan.
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Partnerships with universities, the National Center For Scientific Research (CNRS), and with private companies.

Principal laboratory publications

- Galvani S et al: A key role for MMPs and neutral sphingomyelinase-2 in transplant vasculopathy triggered by anti-HLA antibody. Circulation 2011, 124:2725
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