

Cardiovascular diseases: the battle gets more intense

Famous the world over, research at Toulouse in the domain of cardiovascular diseases is becoming more organized in a new research center focusing on both metabolic and cardiovascular diseases – the second cause of death in industrialized countries.



>>> Angelo PARINI, director of I2MR (©Inserm – G. Esteve) and Dominique LANGIN, head of the metabolism department (©Inserm - P. Latron)

Researchers at Toulouse study the risk factors that lead to cardiovascular diseases. These studies focus on molecular mechanisms, pre-clinical research on animal models, as well as clinical research and epidemiology.

A unique structure

Most of the teams at Paul Sabatier working in the domains of metabolic and cardiovascular diseases are today grouped at the Institut de Médecine Moléculaire de Rangueil (I2MR). This institute was created in January 2007 by Inserm and UPS, and will soon change its name to “Institut des Maladies Métaboliques et Cardiovasculaires” (I2MC).

The I2MC will boast three new teams. The first two (“Lipoproteins, Lipidic Transport and Dyslipidemies” and “Signaling and Phosphoinositides in Hematopoietic cells”) come from the Purpan site and the third comes from Paris. The arrival of these three teams at I2MC will allow researchers to put forward a unique project focusing on risk factors, in particular obesity, diabetes, dyslipidemies, and how they lead to cardiovascular complications such as thrombosis, and renal and cardiac failure.

Partnerships

The different teams have established numerous national and international collaborations through ANR and European projects in the fields of atherosclerosis, cardiac and renal failure, and cellular therapy of cardiovascular diseases. Collaboration with industrial laboratories (such as Sanofi-Aventis, Servier and Glaxo-SmithKline) and with local

companies (like Urosphere; Physiogenex and Ambiotis) are also important.

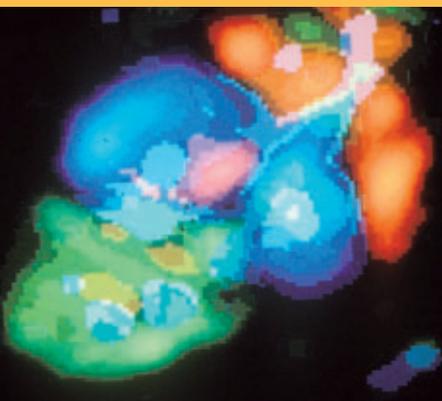
The second cause of death

In this magazine, we present the main fields of research in Toulouse focusing on cardiovascular diseases. A variety of topics is looked at, from atherothrombosis (where blood vessels become progressively blocked) to studies on the heart and the influence of hormones, which play a key role in blood circulation. Our research still needs to explore many other aspects of cardiovascular disease with a view to reducing the morbidity and mortality related to these pathologies

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I2MC: Institut des Maladies Métaboliques et Cardiovasculaires/ Institute of Metabolic and Cardiovascular Diseases



>>> IRM image of the heart (©Inserm – D.Michel).

headline

A better understanding of heart failure



>>> Jean-Michel SENARD, UPS professor, head of the Molecular and Clinical Pharmacology of the Autonomic Nervous System team at I2MR (Inserm/UPS lab) and physician in the Department of Clinical Pharmacology at Toulouse University Hospital.

By recording the activity of sympathetic nerves using a new technique, specialists from the Toulouse Rangueil Hospital now have a better understanding of heart disease and how to treat it.

Heart failure is the final stage in most cardiovascular diseases. Despite huge advances over the last 20 years, the prognosis for heart failure remains bad with a median life expectancy of just four years, up to 150,000 hospital stays and 32,000 deaths per year in France.

Heart failure is characterized by the activation of humoral and neuronal systems like renin-angiotensin-aldosterone and sympathetic systems respectively. The sympathetic nervous system, through noradrenaline release and a large variety of adrenergic receptors, regulates vascular tone and intrinsic heart functions (such as heart rate, contractility and excitability). One of the research axes of our team focuses on the mechanisms underlying sympathetic hyperactivity during heart failure and how important it is to measure this activity for understanding the effects of drugs or to evaluate prognosis. In fact, sympathetic activation is, in the short term, a mechanism that compensates for the fall in cardiac output. However, over the more long term, sympathetic hyperactivity leads to the progressive worsening of heart failure and increased risk from sudden cardiac death at the severe stages of the disease.

Gold standard

Thank to the expertise of Atul Pathak, we have developed a technique in the Department of Cardiology of the Toulouse University Hospital that is available in only a few laboratories worldwide and considered as the gold standard for testing sympathetic nervous system activity. This technique, called muscle sympathetic nerve activity (MSNA), consists of recording the activity of sympathetic fibers using an electrode inserted within the fibular nerve. Quantifying sympathetic activity involves calculating the number of bursts per minute, for instance.

This research has yielded important results so far. It first allowed us to conclude that a rise in sympathetic activity during heart failure leads to an increase in

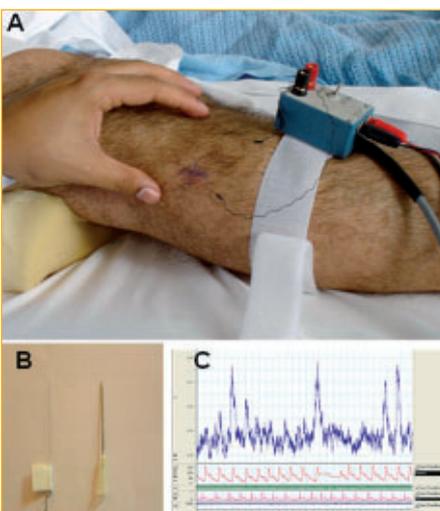
renal failure and anemia. These two anomalies are frequently observed in heart failure patients and have been identified as bad prognosis factors. The mechanisms by which anemia and renal failure further increase sympathetic activity during heart failure are not totally understood but involve activation of chemoreflexes. These reflexes induce changes in lung ventilation in response to variations in oxygen and/or carbon dioxide concentrations in blood. They also modulate sympathetic activity and thus contribute to cardiovascular homeostasis.

Another finding concerns inotropic drugs used in acute decompensated heart failure. These drugs improve heart contractility but those that increase sympathetic activity have all been shown to be associated with an increased risk of rhythm disturbances and of sudden cardiac death. We have recently demonstrated that only one drug from this therapeutic class, levosimendan, significantly decreases sympathetic nerve activity measured using MSNA.

Sudden cardiac death

Sudden cardiac death, after rhythm disturbances, is frequent during heart failure and avoids the use of implantable defibrillators. In the frame of a large clinical study we will try to correlate the risk of sudden death (using discharge from defibrillator as a surrogate) and the level of sympathetic activity measured using MSNA. The aim of this study is to determine the clinical characteristics of patients who absolutely need such a devices, which are expensive.

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>>> A: Position of the electrode for recording sympathetic nervous activity at the fibular nerve in humans.
 B: details of the microelectrodes used;
 C: A typical example of a MSNA neurogram showing various bursts. The number of bursts per minute is used to quantify sympathetic activity.

Blood platelets, targets for antithrombotic drugs

Myocardial infarction and stroke, which are caused by arterial thrombosis in the heart and brain, represent one of the most common causes of mortality and morbidity in the western world. In many cases, arterial thrombosis is a major complication of atherosclerosis.



>>> members of Bernard PAYRASTRE'S Platelet Production and Functions, Signaling and Phosphoinositides group, which will join I2MC (I2MC, joint UPS/Inserm lab).

Blood platelets play a key role in the pathogenesis of thrombosis. In physiology, these small anucleated cells originating from megakaryocyte fragmentation, rapidly interact and aggregate at the site of an injured vessel wall to form a thrombus and lead to the formation of a fibrin clot that allows bleeding to stop. Thus, functional platelets are crucial for promptly stopping bleeding. Inherited or acquired platelet defects are therefore associated with mild to severe bleeding disorders. Under pathological conditions, such as rupture of an unstable atherosclerotic plaque, platelets become activated and can form an occlusive thrombus that prevents oxygen from reaching the brain or heart, which results in myocardial infarction or stroke.

The pharmacological control of platelet function is critical in preventing such thrombotic complications. Antiplatelet medication is also used to prevent thrombosis during angioplasty, particularly during coronary artery stenting. Currently, thienopyridines, in combination with aspirin, are the treatment of reference for controlling platelets.

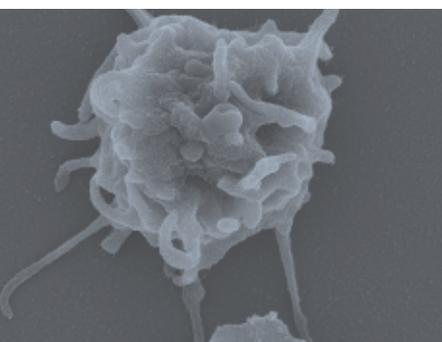
Hemorrhagic risk

So far antiplatelet drugs have been used to target the mechanisms of platelet activation. These treatments do reduce the mortality and morbidity in different groups of patients but their efficiency still has to be improved. Indeed, many problems need to be solved, including drug resistance, efficacy and safety (hemorrhagic risk), dosage, administration requirements and combination therapy. Importantly, none of the current therapies adequately meets the most sought after requirement, which is namely the ability to inhibit platelet contribution to thrombosis without increasing bleeding. Therefore, novel, improved antiplatelet therapies are needed to efficiently prevent thrombosis without increasing the risk of hemorrhage. The development of such agents presupposes an accurate understanding of

the complex mechanisms involved in platelet activation, aggregation and thrombus formation. Indeed, specific membrane receptors and/or downstream intracellular signaling enzymes represent potential antithrombotic drug targets.

Protected mice model

Our group is investigating the mechanisms of signal transduction involved in the different steps of platelet production and activation, particularly by using genetically modified mouse models. We have shown that invalidation of specific enzymes in lipid metabolism (kinases and phosphatases) selectively in megakaryocytes and platelets can protect mice from occlusive thrombus formation upon carotid injury without increasing the hemorrhagic risk. Our aim is to find new targets for antithrombotic drug targets and to propose new risk markers for thrombosis as well as molecular markers that will allow us to monitor the efficiency of antiplatelet drugs in the clinic. The collaboration between our research group with the cardiovascular and the neurovascular departments at Rangueil Hospital as well as the Department of Vascular Medicine and the Laboratory of Hemostasis allowed us to set up a translational research center and transfer advances in basic research into the medical field. This strategy has also allowed us to set up new methods to identify and characterize genetic and acquired platelet dysfunctions leading to hemorrhagic syndromes. Finally, a better understanding of the molecular processes of megakaryocyte maturation and platelet production, still poorly known, should allow potential interventions that correct or hijack processes such as biogenesis of platelet granules, which contain a number of substances involved in hemostasis, thrombosis but also inflammation and healing.



>>> A scanning electron micrograph of an activated blood platelet.

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headline

Understanding the protective effect of estrogens on metabolic and vascular diseases



>>> Jean-Francois ARNAL and Pierre GOURDY, professors at UPS and researchers at the Institut de Médecine Moléculaire de Ranguéil (I2MR, UPS/Inserm lab)
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Estrogens are produced by the ovaries before the menopause. Beyond their crucial role in reproduction, these steroid hormones have numerous effects, in particular on the cardiovascular system and in energy metabolism.

Before the menopause, women are less prone than men to developing metabolic diseases, such as diabetes type 2, but also cardiovascular diseases, suggesting that endogenous estrogens have a protective effect.

Furthermore, administering estrogens to animal models prevents the onset of diabetes and atherosclerosis, the main cause of cardiovascular disease.

Demonized hormones

A random trial intervention conducted in 2002 in the United States (Women Health Initiative) showed that, although reducing the incidence of diabetes type 2, these hormones did not confer cardiovascular protection, thereby questioning a belief held for several decades. However, this study was not representative practice because it involved older women (treatment was begun late, on average 11 years after the age of menopause) and thus wrongly "demonized" estrogens!

The aim of our team is thus to understand the mechanisms responsible for the protective effect of estrogens in metabolic and vascular diseases and why these hormones do not confer cardiovascular protection when they are administered far after the menopause.

Delaying ageing

It is known that estrogens can prevent risks of fracture, brought about by bone demineralization. They also prevent the onset of metabolic diseases, like obesity and diabetes, and atheroma lesions, the main cause of cardiovascular disease. Thereby, estrogens could even delay some aspects of ageing, and this probably represents the major challenge when modulating estrogen receptors.

Estrogens do not only concern women, because androgens (the male sex hormones) are partially converted, in many tissues of the body, into estrogens too. Thanks to a new model of transgenic mice that consists of inactivating one of the two trans-activating functions of the estrogen receptor, we recently showed

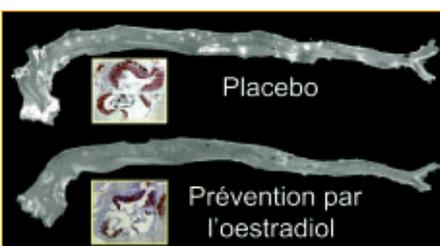
that it is possible to activate this receptor and retain the vasculo-protective effects of estrogens - in particular, in the prevention of atheroma, without producing the classic sexual effects. If, as a famous writer once said, "woman is the future of man", feminine sex hormones could protect the futures of both men and women.

Risk of cancer

The long-term administration of estrogens increases, in a moderate but significant manner, the risk of cancer of the uterus and breast. Molecules that selectively modulate estrogen receptors already exist and are used to treat breast cancer and also prevent bone demineralization, demonstrating the feasibility of the approach. However, they do not confer cardiovascular or metabolic protection.

Based on the results from partial deletion of the estrogen receptor, our strategy derives from the postulate that molecules partially activating the receptor might lead to a new generation of estrogens. This approach requires a better understanding of how the estrogen receptor functions, that is, the in vivo "dissection" of the cellular and molecular targets thanks to the use of integrated models of genetically modified mice. Our ultimate goal is to contribute to the design and/or screening of molecules modulating the estrogen receptor with an optimized benefit-to-risk.

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>>> Atheroma lesions (in white, and then colored red in the inset) in the aorta of hypercholesterolemic mice.

A dangerous duo for cardiac ageing and failure



>>> Jeanne MIALET-PEREZ, Inserm scientist and Nathalie PIZZINAT, CNRS scientist (©Inserm – G.Esteve) at the I2MR (Institut de Médecine Moléculaire de Rangueil, UPS/Inserm)

A duo of molecules comprising monoamine oxydase A and serotonin participates in cardiac ageing and failure.

Heart failure is defined by the inability of the heart to supply sufficient blood flow to meet the body's needs. It is now, in the 21st century, a major public health concern in the west. Despite recent advances in the diagnosis and care of heart failure, the prevalence and incidence of this disease is still growing. It is essentially affects the elderly and around 15 % of individuals over 80 suffer from the pathology.

Cardiac remodeling

Heart failure in the elderly results from an increase in cardiovascular risk factors (including diabetes, high blood pressure and dyslipidemia) but also from age-related intrinsic factors. Heart failure is the terminal stage in the long term remodeling of the heart, characterized by hypertrophy, fibrosis and ventricular dilation. At present, the molecular mechanisms involved in cardiac remodeling associated with ageing are not clearly defined.

During the last few years, our team has focused a large part of its activity on the role of the mitochondrial monoamine oxydase A enzyme (MAO A) and of its main substrate, serotonin, in cardiac remodeling and failure during ageing. Our results have allowed to demonstrate that MAO-A generates large amounts of reactive oxygen species during the degradation of

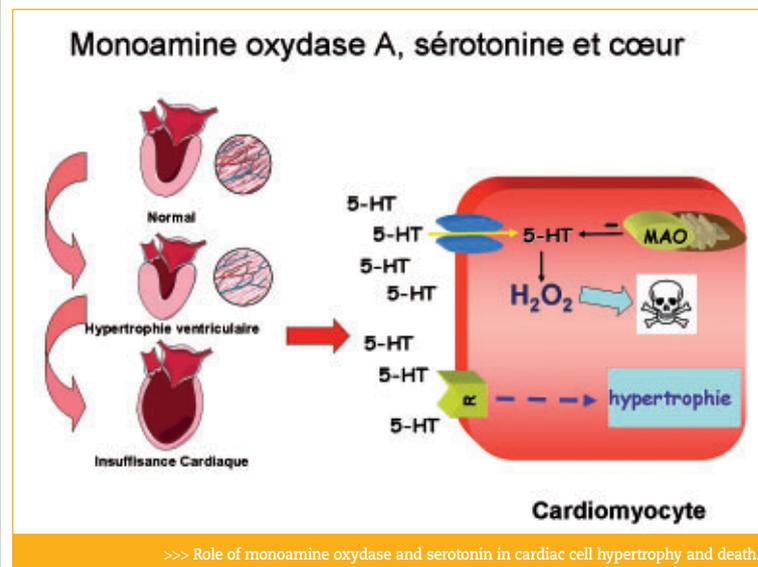
serotonin in the heart, and that this production increases in a very significant way in old animals.

Cell death

In order to determine if the increase in the expression of cardiac MAO could have pathological consequences on the heart, we studied transgenic mice that overexpressed this enzyme specifically in cardiac cells. In agreement with the hypothesis of the deleterious role of MAO and reactive oxygen species in the heart, we observed that an increase in cardiac MAO-A leads to massive death of cardiomyocytes, and to spontaneous heart failure. These results allowed us to identify MAO-A as a new key factor involved in cardiac cell death, and in the appearance of heart failure. On the other hand, we also demonstrated that an increase in cardiac serotonin content, due to a modification of the synthesis and/or the degradation by MAO, plays a key role in cardiac remodeling by two mechanisms: the induction of cardiomyocyte hypertrophy and the reorganization of the extracellular matrix by the activation of fibroblasts. In both types of cardiac cells, the effects of the serotonin involve the activation of the serotonin receptor subtype 5-HT_{2A}.

All these results allow us to identify for the first time the duo MAO-A/serotonin as one of the main factors

involved in cardiac remodeling and failure. These observations make MAO and serotonin receptors 5-HT_{2A} promising and original targets for the pharmacological prevention and treatment of cardiac failure during ageing.



>>> Role of monoamine oxydase and serotonin in cardiac cell hypertrophy and death.

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headline

Stem cells at the bedside of cardiovascular diseases



>>> Angelo PARINI, senior scientist at I2MR (UPS/Inserm lab) and Louis CASTEILLA (Métabolisme, Plasticité et Mitochondries group, UPS/CNRS lab) ©Inserm-G.Esteve

Stem-cell based therapies represent innovative biotherapies for myocardial infarction, cardiac failure and vascular diseases. Toulouse's teams in basic, translational and medical research have joined forces to take up this challenge.

Stem cells are able to self-renew and give rise to different specialized phenotypes. Embryonic and fetus stem cells are considered as totipotent or pluripotent because they display a higher differentiation potential than adult stem cells that are multipotent or unipotent only.

Despite this lower differentiation potential, adult stem cells present unquestionable advantages with respect to embryonic stem cells. Firstly, as they can be used in autologous settings, the risk of rejection is totally avoided. Secondly, their lower differentiation potential limits the risk of tumorigenesis and they are very easy to cultivate in a secure and safe manner. In general, they also pose few ethical problems.

Regenerative potential

Over the last few years, a complementary research consortium has been focusing on understanding the biology of mesenchymal stem cells present in conjunctive tissues and their clinical uses to treat different cardiovascular diseases. Adult mesenchymal stem cells that display mesenchymal potentials and a strong paracrine activity represent promising

candidates for cell therapy and regenerative medicine for central or peripheral ischemic diseases. All these pathologies are characterized by a large decrease in arterial blood supply.

This consortium brings together different teams: Remodelage Cardiaque: Aspects Physiopathologiques et Nouvelles Thérapeutiques from the I2MR (led by Angelo Parini), Stromalab (Louis Casteilla), the Etablissement Français du Sang Pyrénées Méditerranée

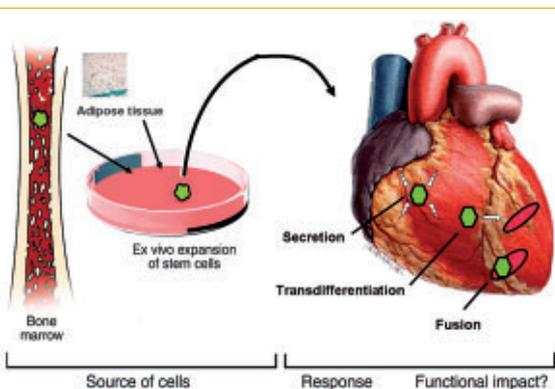
(Philippe Bourin), the functional unit Biothérapie du CIC 9302 (Louis Buscail), and the Service de Cardiologie (Jérôme Roncalli) et Médecine Vasculaire (Alessandra Bura-Rivière) of CHU Rangueil.

Bone marrow and adipose tissue

The teams of A. Parini and L. Casteilla are working on mesenchymal stem cells from bone marrow and adipose tissue respectively. These teams have characterized cell and molecular mechanisms involved in the therapeutic effects associated with these cells and set-up different processes to increase their survival rate and efficiency after transplantation. Thanks to the consortium, new insights from basic science have been efficiently transferred to clinical trials. Thus BONAMI, a multicenter clinical trial on the use of bone marrow derived cells in myocardial infarction is already finished and its results are being published. Moreover, MESAMI, a pilot study, is investigating the benefits associated with the autologous transplantation of bone marrow mesenchymal stem cells in chronic myocardial infarction. Finally, AcellDream is investigating the use of autologous adipose derived stem cells to treat chronic leg ischemia.

According to its expertise in basic science as well as in translational research, our consortium and Toulouse itself are well recognized in the research field of adult stem-cell based therapy. The close link between scientists and clinicians is a major asset for setting up innovative biotherapies.

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>>> Mesenchymal stem cells and cardiac cellular therapy.

From lipids to vascular accidents

How can lipid accumulation in arteries lead to atherosclerosis? A crucial question for a leading cause of death worldwide.



>>> Anne NÈGRE-SALVAYRE, CNRS senior scientist at I2MR (Inserm/UPS) ©G.Esteve - Inserm

Atherosclerosis is a consequence of the progressive ageing of medium and large arteries (such as the aorta, coronaries and carotides). It is characterized by the presence of lipid-rich plaques in the vascular wall. Atherosclerosis is the main cause of cardio- and neuro-vascular accidents (for example, infarctus and stroke), and a leading cause of morbidity and mortality in industrialized countries. A huge number of risk factors are involved in the development of atherosclerosis, in particular ageing, gender (male), familial and genetic factors, pathologies such as diabetes, hypertension and obesity, as well as dietary habits, sedentarity or smoking.

Cholesterol

Lipids are transported in the blood by specific proteins, such as low density lipoproteins (LDL), which transport cholesterol from the liver to tissues. Cholesterol-rich diets increase the plasmatic LDL and LDL-cholesterol levels, and cause atherosclerotic lesion formation.

Atherosclerotic lesions develop in the vascular wall, turbulent blood flow areas where endothelial cells lining the inner vessel wall become more permeable to leukocytes and macromolecules such as LDL. Once in the vascular wall, LDLs are oxidized by reactive oxygen species (ROS), which are continuously produced by vascular cells. Oxidized LDLs are taken up by macrophages which accumulate lipid droplets in the cytosol and are progressively transformed into "foam cells". The accumulation of foam cells constitute the

fatty streaks already visible during childhood in areas predisposed to the formation of atherosclerotic lesions.

The progressive remodeling of early lesions results in the formation of more complicated plaques, characterized by a necrotic lipid-rich core, formed of intra and extracellular cholesterol deposits, macrophages and cellular debris, and

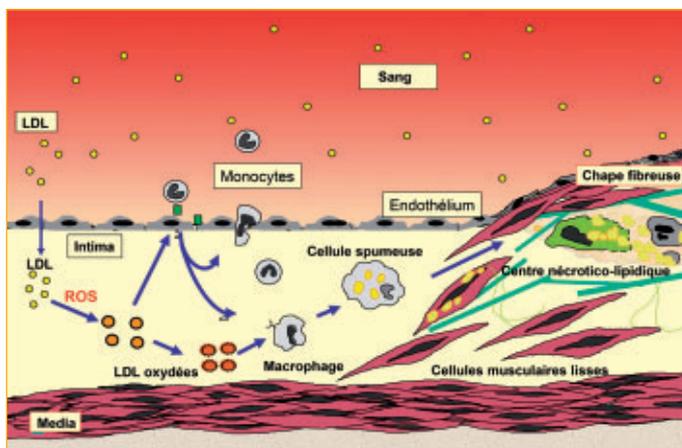
centered by a fibrous cap, which determines the fate (stability or fragility) of the plaque. In some cases, lesion progression may theoretically reduce the diameter of vessels and blood flow, thereby inducing chest pain or cramp. Finally, the rupture or erosion of "fragile" plaques trigger clot formation and thrombotic events, resulting in neuro- and/or cardio-vascular accidents.

Toxic events

Oxidized LDLs play a central role in the formation of atherosclerotic lesions and their evolving to more advanced states. This is due to the fact that oxidized LDL transports and introduces bioactive molecules (oxidized lipids) inside the cells.

Our group has been working for several years on the biological properties of oxidized lipids. We have shown that most oxidized lipids and oxidized LDLs trigger various cellular responses which differ as a function of their local concentration. At low concentrations, these agents trigger mitogenic and inflammatory responses, while at higher concentrations they induce toxic pro-apoptotic responses. For instance, some oxidized lipids bind tissular proteins and modify their structure and function. The accumulation of modified proteins inhibits cellular migration and proliferation and generates inflammatory events. Oxysterols may substitute for cholesterol in cellular membranes, thus modifying membrane structure and inducing cell death. We notably reported that the local presence of oxidized molecules maintains a pro-oxidant environment prone to fragilizing vascular cells. The effects of oxidized lipids can be observed in vivo in atherosclerotic lesions.

An important challenge for our team consists in developing natural or synthetic pharmacological agents able to block the deleterious effects of oxidized lipid mediators, which should limit the development of lesions and stabilize plaques, thus preventing or reducing the occurrence of atherothrombotic events.



>>> Schematic mechanism of atherosclerotic plaque formation.

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Obesity and heart failure



>>> Michel GALINIER, UPS professor and Philippe ROUET, senior INSERM scientist, heads the Obesity and Heart failure: Molecular and Clinical Investigations team at the Institut de Médecine Moléculaire de Rangueil (I2MR, Inserm/UPS).

Studying activated genes or proteins in individuals with cardiovascular risk factors is a promising field of research. Two distinct research axes are being developed. The first focuses on the regulation and functional analysis of activated genes in obese patients to understand the molecular mechanisms leading to cardiomyopathies. The second aims at identifying blood molecules that could reveal the ongoing development of “silent” heart failure.

The prevalence of obesity is increasing across the world with over 300 million people suffering from the ailment. Obesity is linked to an elevated cardiovascular morbi-mortality. Only a few studies have focused on the cardiomyopathy of the obese, thought to be secondary to arterial hypertension and metabolic disorders. However, obesity is an important risk factor for sudden death and heart hypertrophy that is far greater than the expected rate due to arterial blood pressure. Moreover, it has recently been shown that obesity is an independent risk factor for heart failure: a body mass index over 30 kg/m² doubles heart failure risk. Underlying mechanisms are poorly known but probably involve adipose tissue secretions (such as fatty acids and adipokines).

Heart genes

To study how the heart adapts to obesity, our team has studied the heart transcriptome to look for regulations of gene expression induced by obesity in a nutritional model of obesity generated by 9 weeks on a high fat diet. We have shown heart gene regulations that indicate the onset of early mechanisms leading to heart remodeling in the obese. This work was further conducted in humans using microarray chips.

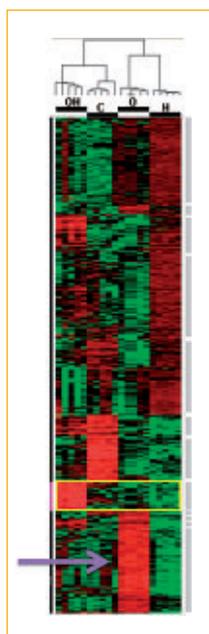
Preventing lipid accumulation in the heart

Analysis of the results clearly shows that the molecular picture of the heart in the obese is very specific and strongly differs from what is observed in hypertensive or obese-hypertensive patients. Computer analysis of differentially expressed genes reveals a set of genes encoding for proteins not yet characterized. Amongst these, we identified new proteins with putative important functions: a new transcription factor and a new apolipoprotein that we named Apolipoprotein O (ApoO). We have observed that ApoO expression is induced in the hearts of diabetic patients and that ApoO expression is strongly correlated with apoptosis-related gene

expression. We are currently investigating the pathophysiological role of ApoO in the heart using cellular models, transgenic mice and human heart samples. ApoO could represent a pharmacological target to prevent heart pathological remodeling.

Blood biomarkers for pre-heart failure

In addition, we are investigating for new and early heart failure (HF) biomarkers. Over 60 million patients around the world have HF. HF is a progressive disease that evolves from an asymptomatic phase (asymptomatic left ventricular dysfunction: ALVD) to severe stages that are difficult to treat. Identifying ALVD patients could prevent symptomatic HF development by early care and treatment of these patients. However, identifying ALVD is impossible today in general care practice. Patient history and physical examination is generally not sufficient for ALVD diagnosis, which requires specialized techniques such as echocardiography. We looked for blood ALVD biomarkers using transcriptome, metabolome and proteome analyses in patients with cardiovascular risk factors. Our results have already revealed a set of ALVD biomarkers (patenting in progress). Understanding the origin and the physiopathological role of these biomarkers could also set up a base for more fundamental investigations. However, the immediate spin-off of these studies should be a routine large-scale identification of ALVD patients, especially in ageing populations. Routine large-scale screens should allow for early care of ALVD patients and prevent HF development, which despite recent advances in treatments, remains difficult to control at its advanced stages and leads to a large number of deaths.



>>> Hierarchical clustering representation of human heart transcriptome analysis. Five patients per group were analyzed. OH: obese-hypertensive; C: control; O: Obese; H: hypertensive. Overexpressed genes are in red, underexpressed genes are in green. Obesity induces overexpression of a specific set of genes (arrow) before “symptomatic” heart failure sets in.

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