Cytochrome P450 subfamily 2J polypeptide 2 (CYP2J2) plays a role in the pathogenesis of preeclampsia and is a potential candidate for the disturbed uteroplacental remodelling, leading to hypertension and endothelial dysfunction concludes a recent article in Circulation. The last author of this article is Ralf Dechend, MD, group leader, Experimental and Clinical Research Centre, Charité Medical Faculty and the Max-Delbrück Centre for Molecular Medicine, Berlin, Germany, and senior physician, HELIOS Clinic Department of Cardiology and Nephrology, Berlin. The team, including Florian Herse, PhD, Dominik M. Müller, PhD (see http://circ.ahajournals.org/content/121/24/f139), and others, performed microarray screening of placenta and decidua (maternal placenta) from 25 preeclamptic women and 23 control subjects and found that CYP2J2 was upregulated in preeclamptic placenta and decidua by tumour necrosis factor-alpha in trophoblasts.

Dr Dechend says, “We started with an extensive gene array analysis from well-characterised preeclamptic patients and controls. To our surprise, only a few candidate genes were consistently upregulated, and CYP2J2 was the most promising candidate. We showed upregulation of the enzyme in the placenta and the metabolised substrates, epoxyeicosatrienoic acids, in the circulation for the first time by a complicated method (tandem mass spectrometry techniques coupled with high-performance liquid chromatography) before the clinical syndrome. We can also show that a special epoxyeicosatrienoic acid can be metabolised to a thromboxane analog, which is one of the most powerful vasoconstricting agents. This chain of events has not previously been demonstrated. Epoxideicosatrienoic acids have been regarded as positive vasodilating metabolites, but we were the first to show that the context determines whether they are protective.

“Preeclampsia is a vascular disease, linking hypertension and immunology, and decades later, mother and child have a higher risk of cardiovascular disease. It is an excellent example of an interdisciplinary disease involving obstetricians, nephrologists, cardiologists, reproductive immunologists, and physiologists. It has a high prevalence, high morbidity and mortality, an enormous emotional and economic burden, and no therapy, and its cause is unknown.”

The opportunity to conduct research in preeclampsia arose “by chance” for Dr Dechend. He explains, “Our institute had a clinical interest in preeclampsia, and I was asked, together with Gerd Wallakut, who worked on activating antibodies against G-coupled receptors, to carry out some molecular biology experiments. The results were published in Circulation in 2000, in an article titled “AT(1) Receptor Agonistic Antibodies From Preeclamptic Patients Cause Vascular Cells to Express Tissue Factor,” accompanied by an editorial by Professor Jim Roberts, MD, of the Magee-Womens...
Dr Dechend with his wife Susanne, an intensive care nurse, and 2 daughters. He says, “My daughters changed my life more than I ever thought and I have changed my work timetable so I am at home at 5:00 to 5:30 PM, several times a week, and I go back to the computer in the evening.” Outside medicine, his interests are his family, travelling, and sport. Photo courtesy of Dr Dechend.

Research Institute, Pittsburgh, PA. Dr Dechend says, “Professor Roberts invited me to Pittsburgh, one of the best and largest preeclampsia research units in the United States, and to a special conference called ‘Tox Talk,’ and from then on I was hooked on preeclampsia.”

**Demonstrating That Autoantibodies Are Responsible for the Increased Angiotensin II Sensitivity in Preeclampsia**

Dr Dechend says that his most important articles are those showing binding of autoantibody to the angiotensin II type 1 (AT1) receptor and the molecular pathway linking AT1 receptor activation and inflammation, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation, and reactive oxygen.  

This work was among his most enjoyable research because of the feedback received for his work on the autoantibodies against the AT1 receptor. He comments, “This hypothesis triggered a lot of research.” Other important articles for Dr Dechend are a 2001 article in *Circulation*, which was the first report showing the anti-inflammatory effects of statins in hypertension-induced end-organ damage; an article in *Hypertension* in 2008, describing a rat model for preeclampsia with autoantibodies and altered trophoblast invasion, similar to the human situation; and another article in *Circulation* in 2007 on endothelial cell-specific, functional knockout of NFκB, showing that NFκB in the endothelial cell is important in inducing the hypertension-induced end-organ damage. In 2011, Dr Dechend and his group showed that autoantibodies are responsible for the increased angiotensin II sensitivity in preeclampsia. “This was the first study that could explain this observed feature in human preeclampsia,” he says.

An article that Dr Dechend says “challenged our work on preeclampsia” was published in 2003. Sharon E. Maynard, MD, and her colleagues looked at how excess placental soluble fms-like tyrosine kinase 1 might contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. Dr Dechend says, “Since then we have had a close collaboration and changed our understanding of preeclampsia.”

**Working Under 2 Contracts as a Physician Scientist**

Dr Dechend was born in Hannover, Germany, and his parents, both of whom are disabled, have inspired him over the years. He says, “My mother had poliomyelitis and my father had bone tuberculosis after World War II. They manage their lives perfectly and take less sick leave than me.” While studying medicine at the Medical School of Hannover from 1986 to 1993, Dr Dechend became interested in cardiology and hypertension when he worked in the haematology lab, and his dissertation focused on the fibrinolytic activity of low molecular weight heparins. The interest developed when he spent a year studying paediatric cardiology at the University of Liverpool, Liverpool, England. Dr Dechend also spent 6 months in his final year at Brown University, Providence, RI.

Dr Dechend’s first job as junior doctor at the Franz-Volhard Clinic, Charité, highlighted the need for collaboration between basic science and the clinic because many of the senior physicians had an affiliation with the Max-Delbrück Centre. From 1998 to 2002, Dr Dechend worked as a scientific coworker at Charité and HELIOS Clinic under Professor Rainer Dietz, MD, PhD. He achieved his internal medicine boards in 2002, his habilitation on the meaning of transcription factor NFκB in inflammatory reactions in the pathogenesis of arteriosclerotic and hypertensive vessel damage in 2003, and his boards in cardiology in 2007.

Dr Dechend reflects on the impact his mentor, Professor Friedrich Luft, MD, PhD, had on him for his “incredible knowledge, absolute dedication, passionate curiosity, fantastic teaching, and integration of basic science to clinical medicine” and for opening his eyes to look at hypertension in pregnancy. “He felt responsible for me and taught me to never forget this for our staff.”

A notable event that helped shape the direction of Dr Dechend’s career was meeting Dr Müller, a postdoc in Professor Luft’s group. Dr Dechend says, “We became close friends, teamed up, and finally founded our own group, with a translational approach, with the focus on investigating the renin-angiotensin system, the immune system, and how both systems cause hypertension-induced, angiotensin II-related target organ damage. We have chosen preeclampsia as a model disease because dysregulation of the renin-angiotensin system, immunology, hypertension, and severe end-organ damage are characteristics of this disease.”

Dr Dechend has also had a long collaboration with Professor Anne Catherine Staff, MD, PhD, from Oslo, Norway, “who is a distinguished clinical scientist and has built up an ‘excellent biobank from preeclamptic patients.’”
A key interest for Dr Dechend has been the molecular mechanism leading to hypertension-induced end-organ damage. The research he has carried out with his group has involved uncoupling hypertension from the end-organ damage, showing that inflammation, especially NFκB, is essential; the role of chlamydia and anti-inflammatory effects in end-organ damage; the role of immune system-activating autoantibodies against the AT1 receptor in preeclampsia and kidney rejection; the role of regulatory T cells; the establishment of a novel rat model for preeclampsia that resembles the human pathology; and the establishment of a large biobank (in collaboration with Professor Staff) to identify novel biomarkers and genes involved in preeclampsia (gene array, microRNA sequencing).

Dr Dechend’s work as an independent group leader with Dr Müller at the Experimental and Clinical Research Centre takes up ≈ 40% of his time. His work is funded by his institute, the German Research Foundation, industry, and the Federal Ministry of Economics. “Funding is tight, and you have to publish within 2 to 3 years, so you do not start risky projects,” says Dr Dechend. “It is crucial that the academic reward system encourages collaborations and innovative research.” For the remaining 60% of his time, Dr Dechend works as a senior physician at the HELIOS Clinic Department of Cardiology and Nephrology. Like many physician scientists in the United States, he works under 2 different contracts. He also has teaching roles in cardiology and clinical pharmacology, and he particularly enjoys his role in organizing 3-day clinical visits for young basic scientists from the Max Delbrück Centre’s International Helmholtz Research School Translational Cardiovascular and Metabolic Medicine (TRANSCARD) Programme to help them transfer their research from bench to bedside. Dr Dechend says, “Physician scientists are a species between clinic and basic science. It is important to give them a stable position in the research field.”

References

Mark Nicholls is a freelance medical journalist.
Funding Projects for Former Weapons Scientists to Redirect Their Talents to Peaceful Activities and Integrate into the International Scientific Community

Cardiovascular research scientists funded by the International Science and Technology Centre describe the funding and their research to Jennifer Taylor, BSc, MSc, MPhil.

The International Science and Technology Centre was set up in Moscow, Russia, as an intergovernmental organisation to provide Russian and Commonwealth of Independent States former weapons scientists, particularly those with knowledge and skills related to weapons of mass destruction, opportunities to redirect their talents to peaceful activities and integrate into the international scientific community. The principal way in which it meets its objectives is through the Science Project Programme, which solicits scientific project proposals from institutes throughout the Commonwealth of Independent States and provides funding and logistic support to project teams. Projects are conducted with foreign collaborators who ensure that the project goals contribute to the state of the art in the field and that the results will find applications in real problems in basic and applied research.

One of the earliest cardiovascular projects funded by the International Science and Technology Centre, from 1993 to 1998, was titled “Synthesis and Studies of Properties of Cardiac and Antitumour Drugs Using the Methods Developed at Producing Weapons of Mass Destruction.” This project was led by the Institute of Problems of Chemical Physics in Chernogolovka, Russia, which used its expertise in the development of explosives and propellants for ballistic missiles. The foreign collaborating institutes were the III Department of Internal Medicine, University of Roma “La Sapienza,” Rome, Italy, and the Department of Chemistry, University of Wisconsin, Milwaukee, WI.

Recent Projects Funded by the International Science and Technology Centre
New Approaches to Prophylaxis and Treatment of Myocardial Infarction: Apoptosis Regulation
Professor Galina D. Mironova, MD, head, Lab of Mitochondrial Transport, Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Pushchino, Russia, was the lead scientist for this project, which was funded from 2005 to 2011. She says, “The project was intended to help remedy an important social problem, ie, to give the scientists and engineers from the Institute of Immunological Engineering who fulfilled earlier state orders from the Ministry of Defence an opportunity to reorientate their scientific interests. The project enabled them to apply their accumulated experience towards carrying out fundamental and applied studies connected with the international research community.” Weapon scientists from the Institute of Immunological Engineering collaborated with the Institute of Theoretical and Experimental Biophysics on the project.

Two leading foreign scientists, Professor Nils-Erik Leo Saris, PhD, from the University of Helsinki, Helsinki, Finland, and Professor Michel Ovize, MD, PhD, from the Université Claude Bernard, Lyon, France, collaborated with Professor Mironova’s lab during the project. Professor Mironova says, “The foreign collaborators reviewed project documents, including progress and final reports, provided recommendations for conducting common research, and discussed the results during joint workshops in Lyon and Helsinki.”

Professor Mironova’s project qualified for the funding because her lab is a pioneer in the isolation of the mitochondrial ATP-dependent K⁺ channel from tissues and the detection of a natural mitochondrial ATP-dependent K⁺ channel activator. The main aim of the project was to develop new approaches for the prevention and treatment of myocardial infarction using natural channel modulators.

The project included preclinical investigations of the cardioprotective effect of uridine and uridine monophosphate, which are metabolic precursors of the mitochondrial ATP-dependent K⁺ channel activator, uridine diphosphate. These preclinical studies were carried out jointly with scientists from the Institute of Immunological Engineering.
who conducted immunochemical studies to detect the mitochondrial ATP-dependent K\(^+\) channel in mitochondria and obtain specific antimitochondrial ATP-dependent K\(^+\) channel antibodies.

Synthetic activators of the mitochondrial ATP-dependent K\(^+\) channel have been found to have cardioprotection properties, but the mechanism of the protective action is not clear. In an experimental rat model of acute myocardial infarction, the group has shown that the precursors of uridine diphosphate have pronounced antiarrhythmic, antifibrillatory, and anti-ischaemic effects by decreasing the size of necrosis.\(^1\),\(^2\)

In addition, the group studied the structure of the mitochondrial ATP-dependent K\(^+\) channel, its mechanisms of function and regulation, and its role in the experimental animal's adaptation to hypoxia. A study of the channel structure showed that it has homology with the precursor of calregulin and is localised in the mitochondria. Specific polyclonal antibodies to the channel protein inhibited mitochondrial ATP-dependent K\(^+\) channel activity, and mitochondrial ATP-dependent K\(^+\) channel activity was significantly increased in the mitochondria of rats that were highly resistant and adapted to hypoxia in comparison with animals with low resistance.\(^3\)

References


Modelling the Development of Clots in Blood Vessels and the Resultant Abnormalities in Haemodynamics

Professor Maxim G. Khramchenkov, PhD, professor of Kazan (Volga region) Federal University and director, Research Centre of Mathematics and Mechanics, Kazan, Russia, is the lead scientist of this project, which has been ongoing since 2008.

Professor Khramchenkov says, “The project kernel consisted of using accumulated data and methods in the mechanics of multiple-phase flows in porous media. We described and simulated these data numerically to calculate and study the main mechanisms of clot development using computer experimental methods.”

The goal was to calculate the process of clot formation and assess the risk of clot detachment. An original model of solution flow in a porous medium with achemically active matrix was developed as a prototype. A clot was simulated and a special factor was introduced to allow consideration of abnormalities in the process of healing in the vessel wall. Additional nonuniformly distributed strains over the whole supramolecular matrix emerged as the clot continued growing. When the limit values were exceeded, the clot (or its piece) detached. The transport features of the intraclot space were investigated using nuclear magnetic resonance.

During the project implementation period, new physical and mathematical models for flow processes and dissolving, precipitation, and swelling processes, and the effects of impurities on solubility and precipitation were developed.

The foreign collaborators were Claudio Gallo, PhD, senior research investigator, Centre for Advanced Studies, Research and Development, Sardinia, Macchiareddu, Italy, and Rustem L. Litvinov, PhD, senior research investigator, Department of Cell and Development Biology, School of Medicine, University of Pennsylvania, Philadelphia, PA.
The project arose from the urgent need to find new polymers that could be used as coverings on metal stents. Efforts to decrease the risk of stent thrombosis have focused on developing polymers with higher biocompatibility or an ability for biodissolution. This project screened haemo-compatible (ie, not provoking the formation of thrombi, activating the blood clotting system, producing negative reactions to protein and formed elements of blood, or causing harmful immune effects) polymer coverings on metal surfaces.

The goals were to develop synthetic polymer coverings for short- and long-term contact with blood and to develop new thromboresistant polymer coverings for medical devices that come in contact with blood.

Biocompatibility was assessed by subcutaneous implantation of tested materials in experimental animals. Professor Hovhannesyan says, “These studies were needed because implantation of artificial materials into a living organism usually causes acute and chronic inflammatory processes, and the degree depends on the biocompatibility of implants.”

A number of haemocompatible polymer materials were developed during the project and the researchers found that following in vitro and in vivo experiments, a vinyl acetate copolymer with itaconic acid was the best covering for metal stents. During a 3-month period of observation, this polymer covering did not resolve in vivo and did not cause significant changes of blood formed elements, thrombi formation, tissue damage, or harmful immune or toxic effects. Professor Hovhannesyan says, “This covering has been proposed for preclinical testing.”

The 4 foreign collaborators on the project were based at the University of Pisa Medical School, Pisa Italy; the Department of Biotechnology, Centre for Chemistry and Chemical Engineering, Lund University, Lund, Sweden; the Karl-Winnacker-Institute of DECHEMA, Frankfurt am Main, Germany, and the University of Coimbra, Coimbra, Portugal.

Jennifer Taylor is a freelance medical journalist.