Atherosclerosis is a slow-progressing, life-threatening condition in which fatty deposits accumulate in blood vessel walls and develop into thick plaques. Although these early stages of the disease generally progress asymptptomatically and can develop over decades, if and when a plaque eventually ruptures, it can cause a thrombus that blocks blood flow and may cause death within minutes.

Over the last 3 decades, Alain Tedgui, Director of the Paris Cardiovascular Research Center (PARCC), has studied nearly every step of the disease, including how blood pressure and flow influence cell signaling, gene expression, and the deposition of lipids in artery walls,1–4 how inflammatory processes perpetuate the condition,5–8 and how, when plaques rupture, they release thrombogenic microparticles.9,10

In a recent interview with Circulation Research, Tedgui explained that he maintained this wide diversity of research interests by doing science the French way—training excellent scientists, giving them independence, but keeping them close. He also emphasized that maintaining such diversity is the key to keeping an open mind and making the most interesting discoveries.

Tedgui is unquestionably a world leader in atherosclerosis research. But surprisingly, he started out with the intention of becoming a mathematician. Quickly realizing his true calling, he managed to turn a PhD in theoretical fluid mechanics into experimental expertise in arterial wall biology, and never looked back.

Where Did You Grow Up?
I grew up in the city of Oran in Algeria, North Africa, which at the time was French. And I left when it became independent in 1962. I was eight-and-a-half years old, and we moved to Paris, France, where my father already had some family.

Tell Me About Your Family?
I am from a Jewish family. I have a younger brother and older sister. I’m in the middle. My father was a carpenter. He left school and started working at a very young age. My mother also left school early. She was a seamstress in a factory, but she stopped working when she had children.

How Did Your Interest in Science Develop?
Because my parents both left school early, but were dynamic (my father created his own small business as a carpenter when they arrived in Paris), they were committed to giving their children the highest education they could. So, it was important that we were successful at school.

I was good at mathematics and science. And, after my high school degree, my parents really wanted me to enter medical studies. But I did not. I was a bit stubborn and I refused. Instead, I continued in mathematics.

I studied for a degree in applied mathematics, a master’s degree in theoretical fluid mechanics, and then a PhD in fluid mechanics. But I had come to realize I was not a mathematician. It was not my way. I was really interested in biology. So, during my master’s degree, I took courses in biomechanics and then my PhD was in biomechanics applied to collapsible tubes, which related to the elasticity of arteries.

For my postdoctorate fellowship, I went to London, to Imperial College, and joined professor Colin Caro who was running the Physiological Flow Studies Unit. It was really the start of vascular biology in the 1980s. He was interested in the effect of flow on arteries. In fact, he was the first person to show that low shear stress in arteries was associated with atherosclerotic plaque formation. Working in his laboratory was a nice bridge between my training in theoretical fluid mechanics and experimental work. I was working on mechanisms of low-density lipoprotein—cholesterol—accumulation in arteries, which is the first event in atherosclerosis, and was learning experimental techniques in rabbits. That’s how I ended up doing biomedical research.

So Your Parents Almost Got Their Wish?
Yes!

Then You Returned to Paris?
Yes, to the Paris Hospital Lariboisière where I started my career. I was recruited in 1983 and had a position that would be the equivalent these days of an Assistant Professor at INSERM (the National Institute for Health and Medical Research). In 2000, I became Director of the laboratory and then I stayed as Head of Department.
Tell Me How Your Atherosclerosis Research Has Evolved Over the Years From Hemodynamics to Cellular Processes and Immunology

When I came back to Paris from London, I set up my own group and started studying mechanotransduction, which is how mechanical forces are translated into a biological response. So I was interested in intracellular signaling associated with mechanical forces.

I set up a new method of organ culture for arteries. We were able to isolate a segment of artery and culture it for several days under different flow or pressure conditions. I recruited a post doc from Canada—Stephanie Lehoux—and we published several articles, some in Circulation Research, using this organ culture model and showing the effect of pressure and flow on several signaling pathways.

The second area, which I started in parallel and which was later continued by a researcher in the laboratory, Chantal Boulanger, related to microparticles. I had a friend, Jean-Marie Freyssinet, who was a membrane biochemist, and he had discovered how the cell membrane produces microparticles. He also determined how to trap and quantify these microparticles in patients with HIV. I thought that we could apply the same techniques in atherosclerosis patients because the plaques are full of cell debris—the necrotic cores—and it seemed possible that these might be accumulations of microparticles from endothelial and immune cells. And indeed they are.

Interestingly enough, the microparticles have phospholipids on their external surface that are normally found on the inside of cell membranes. In that position, they are accessible to coagulation factors, so we hypothesized that the microparticles present in the human plaques might participate in the formation of a thrombus when the plaque ruptures and the microparticles are released into the circulation.

In 2001, we also published an article in Circulation showing that patients with acute coronary syndromes have high levels of circulating microparticles. Thereafter, we and others found that the higher the level of circulating microparticles, the higher the risk for cardiovascular patients. So, microparticles can also be a biomarker of cardiovascular events.

What About Your Work on Inflammation?

The reason I became interested in inflammation is simple. At the time Russell Ross had come up with the theory that atherosclerotic plaques developed in response to endothelial cell injury, for example, by cholesterol accumulation. He initially thought that endothelial cell injury caused platelets to accumulate, which released PDGF and stimulated proliferation of smooth muscle cells. But, this turned out not to be the case exactly, and he later accepted that inflammation is the major determinant of plaque development and progression.

A lot of laboratories were therefore interested in proinflammatory cytokines and mediators. I thought, ok there are already plenty of people involved in this area, but there are few studying anti-inflammatory mediators. So I decided to look into those.

Together with Ziad Mallat, a young cardiologist in my laboratory, we found that anti-inflammatory cytokines, IL10 and TGFβ, are protective against atherosclerosis. We published these important findings in Circulation Research. And because these are the main mediators of regulatory T cell function, we investigated the role of these cells in atherosclerosis too. That led to a Nature Medicine paper in 2006.

How Do You Juggle All These Different Avenues of Research?

Every time I open a new area of investigation, there is someone who continues the work. The hemodynamic work was continued by Stephanie Lehoux, for example. The microparticle work was continued by Chantal Boulanger. And the work on inflammation and immunity was continued by Ziad Mallat.

That is the French way of doing science. We work all together. It is the sense of laboratory that is important. It is not exactly the same in the United States. There, when you want to become an autonomous investigator and apply for your own grant from the National Institutes of Health, you have to leave the laboratory where you were trained. In France, and the rest of Europe, it is different because you can stay and still be considered independent. Chantal Boulanger and Ziad Mallat, for example, continue to work with me. They have their own groups now, they are independent, worldwide-recognized experts in their fields, but we are still together and that is really fantastic. It is a nice way to work.

Is There One Research Finding in Particular You Are Most Proud of? If So, What?

Oh, I would say the role of anti-inflammatory IL10 and TGFβ because that has opened the way to how different subsets of lymphocytes are involved in the disease. And inflammation is so important. For example, we know atherosclerosis is determined by several risk factors, such as hypertension, cholesterol, a sedentary lifestyle, diabetes mellitus, obesity, and smoking. But in fact all these risk factors, when you look in detail, are probably influenced by inflammation and a person’s immune system.

Even though cholesterol might be the main trigger of atherosclerosis, you can perfectly imagine that exactly the same level of cholesterol in the blood could lead to an exaggerated problem in one patient and no problem in the other—depending on the patients’ different innate and adaptive immune responses to the damage.

Have There Been any Low Points in Your Career?

There were many! Not one in particular, just several failures. What I say quite often to young researchers is that to continue a job in science, you must be able to face defeat and failure in your experiments. That is, of course, absolutely crucial because very often the young think that when you start a project, the outcome is expected and all the experiments should work. After all, their training at university has been to repeat experiments that are well known to work.

But in real research, your experiments are always something new. You absolutely don’t know whether it will work, whether you will finish with exactly what you expect or not. In several cases, of course, it won’t work and then you should be able to stand and face this failure. That is not easy. You must be confident in yourself and you must be able to withstand anxiety because it is an anxiety-inducing and competitive job.

Do You Have any Other Advice for Young Scientists?

Something I also think is important is the juxtaposition of different fields. In my career, I have moved from one field to another many times, and it is by juxtaposing those different disciplines that you make the best or most interesting discoveries.
Do You Still Do Laboratory Work?
Yes, I still do. Of course, I have a lot of administrative work to do, but I do continue to work in the laboratory. I recently supervised a postdoc, and I initiated a new project on the role of microRNAs in atherosclerosis.

Tell Me About It
Because the localization of atherosclerotic plaques is determined by the level of shear stress and because plaques can only develop when oxidized low-density lipoproteins or LDLs accumulate, we have asked whether there are some microRNAs expressed in endothelial cells that respond to shear stress differently depending on the presence or absence of oxidative LDL. We know that microRNAs induced in endothelial cells differ in response to low or high shear stress, so the question was, ok, if you add oxidized LDL, do you see something different, and can this translate in vivo? Indeed, we identified a specific microRNA, miR-92a, which we call atheromiR, that is markedly induced by oxLDL under low shear stress and that is highly expressed in atherosclerosis-prone regions in mice. Furthermore, specific blockade of the microRNA in Ldlr−/− mice reduced endothelial inflammation and altered the development of atherosclerosis. The article has been published in Circulation Research.

Disclosures
None.

References


Alain Tedgui: Atherosclerosis Research à la Française
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