Inflammation in Cardiovascular Disease

Announcer: Welcome to the Mayo Clinic cardiovascular continuing medical education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Friedman: Hello, my name is Paul Friedman, I'm chair of the Department of Cardiovascular Medicine at Mayo Clinic, and I'm delighted to have with me Professor Cornelia Weyand, who is a professor of medicine and immunology in the Mayo Clinic College of Medicine. And additionally, she has an appointment in cardiovascular medicine, and has been a thought leader in inflammation and its impact on multiple conditions, and certainly cardiovascular diseases. So Dr. Weyand, Cornelia, thank you so much for joining me.

Dr. Weyand: Oh, thank you for this opportunity to talk about the most important things there are, the immune system and how it causes inflammation.

Dr. Friedman: Well, I'm really excited to have this conversation with you, because as I think about it, whether we're talking about coronary artery disease, or atrial fibrillation, or congestive heart failure, or obstructive sleep apnea, or really nearly almost any condition, vascular pathology, aorta disease, that we see in cardiovascular medicine, inflammation is at the root cause of it. And I'm wondering if you could make just some comments about that.

Dr. Weyand: Yes, indeed. Inflammation is really a sophisticated response pattern of the immune system, and it was meant to protect the host from infection, from cancer, and of course, to facilitate the repair of injured tissue. So in many disease conditions, this protective machinery turns against the host and causes damage. And atherosclerotic disease is just one example of this, in which we have learned much about the good and the bad of inflammation. How come that inflammation meant to really help the host is turning into a disease process? Well, traditionally, we have looked at atherosclerotic disease as a lipid-driven disease, of course, we know a lot about that. And the lipids are deposited under the endothelial lining, and then the immune system enters that space and tries to deal with these lipids, and that leads, really, to the lesion that then causes the disease process. Another major risk factor, of course, which is shared in common by many aspects of cardiovascular disease is smoking. Again, the common mechanism, how smoking leads to cardiovascular disease is mediated by the immune system. And we know from genetic studies that the aging process is critically important in this connection between aging, inflammation and cardiovascular disease.

Dr. Friedman: So the question is, how do we continue to age chronologically, but not biologically, so that we don't have our inflammatory responses excessively elevated, isn't it?

Dr. Weyand: Well, a new term has appeared, it's called inflammaging. And this term is meant to communicate that the aging process, per se, is associated with the propensity of the immune system to cause inflammation. And the young immune system protects against infection, cancer, repairs the tissue, and can do this in a very balanced way. The old immune system loses the ability to protect against infection, against cancer, and instead of it, it favors inflammatory pathways. And in terms of how can this happen, well, the young immune system is really

focused on its lymphoid side, on its adaptive side, the old immune system becomes much more interested in the myeloid side of things. As underlying science goes in explaining this to us, there is this process that we call clonal hematopoiesis, over lifetime, the bone marrow stem cell accumulates mutations. Some of these mutations enhance the survival capability of myeloid cells, of corneocytes, of monocytes, of microphages, clonal populations appear, and these cause tissue inflammation. There are very elegant studies showing that all what it takes is generating a microphage that has one of the driver mutations of clonal hematopoiesis, and that will enhance inflammation and cause atherosclerotic disease.

Dr. Friedman: Absolutely fascinating, it really is. And every time I talk to you, I begin to realize, inflammation is the center of the human universe.

Dr. Weyand: And indeed it is.

Dr. Friedman: And I wanna get back to a point you made earlier, that is, the classification of coronary diseases in inflammatory condition, what are the drivers of the immune cells that accumulate in atherosclerotic lesions?

Dr. Weyand: So where we have made very good progress is in actually analyzing what sits in these lesions, and we are now able to go in and isolate individual cells, and so-called single-cell technologies, we can take them out, we can analyze their function, we can analyze their transcriptome, we can see which genes they have activated. We can look at promoter regions and see whether they are open or closed. So by doing that, what we see is that there are T cells in the lesions, there are B cells, there are NK cells, and of course there are microphages and there are antigen-presenting cells. So what it looks like is a full sample of the immune system. All aspects of the immune system, both the adaptive ones as well as the innate side of the immune system, are accumulating in these lesions, and the pathologist would call this a typical chronic inflammatory lesion, and the immunologist would say, well, this is a mixture of adaptive cells, T cell, B cells, and innate cells, monocytes, microphages, antigen-presenting cells. We know that there are immune responses going on in these lesions. The fact that the cell populations are older seems to be very important, both for the adaptive side as well as the innate side. What we do not really know well yet is what type of antigens are being handled in these lesions. So are these novel antigens? Are these antigens that are just in visions? And, are they TriBi antigens that we could identify and literally educate the immune system to ignore them? Or, is this actually, simply, of all kinds of antigens that are being recognized in the host? There's some evidence that the latter is the case, so we are seeing viral antigens being presented in these lesions. There's evidence that COVID antigen is being presented in these lesions.

Dr. Friedman: So really, a couple of interesting things you've raised, and I'm gonna come back to COVID in a second, because obviously there's been a huge interest in COVID and cardiovascular disease, but in in light of the inflammatory and potential infectious triggers to some of those, I would say more broadly, besides metabolic syndrome, what do you see as the risk factors that predispose to atherosclerotic disease?

Dr. Weyand: One important risk factors is age, probably the strongest of all risk factors is age. And that has to do with a combination of that the structure of the tissue changes, there is some

tissue breakdown, so the immune system is being asked to come in and clean up. The cleaning function of the immune system is not as well intact as it is in a young host. So we know, for example, that the microphages that need to go into atherosclerotic lesions, they need to be able to eat, they need to be able to efferocytose. So they seem to have a bit of indigestion from all of that eating, and the anti-inflammatory pathways that they usually would have in toning down an immune response are failing, and the proinflammatory pathways that say, okay, respond to this trigger, are getting stronger, so there is a disbalance in this.

Dr. Friedman: So the aging immune system is a major risk factor for atherosclerosis and it fits in, obviously, with age. Are there other ones that you'd like to mention?

Dr. Weyand: Yes, so an interesting new insight is the fact that the immune system not only senses pathogens, it also senses metabolites. So, the immune system participates in surveillance of metabolic environments. So we have seen in our work that the monocytes and the microphages that are circulating, and then enter the tissue site, are very well aware of lipids and lipoproteins, they sense them, and they change their behavior. Immune cells that get into the tissue immune cells are very hungry cells, they need a lot of food, they need to migrate, they need to move, they need to digest, they need to replicate. So, the immune cells have this replicative potential. To do that, to sustain a cell-building program, they need energy resources. And so, they depend highly on the tissue environment in which they are appearing. The tissue environment, interesting enough, is relatively low in glucose. So we have just gone through a study in which we have looked at how inflammatory cells are adapting to a glucose-deplete tissue environment. Well, they are smart, they say, if I can't find sugar, I'll eat something else. So in the case of proinflammatory macrophages, they switch to the utilization of glutamine, they start eating amino acids. So cells that have a program that allow them to adapt to these tissue-metabolic conditions, they are the survivors, they are the winners, they'll be there. And interesting enough for the pro-inflammatory microphages, genetically, they coordinate the ability to switch away from glucose to glutamine, with the ability to present antigen. So the same transcription factor that allows them to survive in the tissue environment, is also the transcription factor that drives the antigen-presenting function. So this is really adaptation to the environment, sensing of the bioenergetic conditions, sensing which fuel is available, adapting to that, and then selecting for cells that can survive in the harsh tissue environment and remain immunostimulatory. And it's very fascinating.

Dr. Friedman: It is very fascinating. And how proper management of the immune system can have such a big impact on cancer and coronary disease. And infections, potentially, in the sense of, during the COVID pandemic, coming back to that topic, we know that individuals with cardiovascular disease, including hypertension, were at particularly high risk for severe infection or death. What are those mechanisms?

Dr. Weyand: That is indeed the case. So, if you look at the 1 million Americans that died from COVID, 85% were older than 65 years old, and there was clearly enrichment of individuals with cardiovascular disease. So we have assembled a cohort of patients that have advanced coronary disease, as an example of this risk group, we have probed their immune system against COVID viral antigen, and found that these patients are not very well capable of making an immune response against the virus. Actually, by giving them a vaccine, that had only a borderline effect

to improve their ability to fight the virus. Interesting enough, this inability to build a strong antiviral response extends to other viruses like EBV virus.

Dr. Friedman: Why is that?

Dr. Weyand: Well, the culprit is the microphage. The microphage of these patients is not very capable of taking up viral protein and present it to the immune system. And we have pinpointed that defect, the microphage actually brings on its surface an immunoinhibitory like it, so the microphage presents a stop signal to the immune system. So patients with advanced coronary disease indeed have a state of immunoparalysis, their immune system is paralyzed in making anti-infectious immunity. The proper term that an immunologist would use is they are immune exhausted, they have immune exhaustion. So that term then implies that something has happened in the past that changed their immune system. So have they been super exposed to antigen? Have they been using up reserve in their immune system, so that they are no longer capable of fighting the virus as a non-cardiovascular individual would do?

Dr. Friedman: So we know then, that patients with cardiovascular disease are more likely to have what you've described as an exhausted immune system. And do we know why that happens? What is it about cardiovascular disease that exhausts the immune system? Or is that to be discovered?

Dr. Weyand: That's to be discovered, that's where the work all goes. I mean, the question is, what's the hen, and what's the egg? Right?

Dr. Friedman: Yeah, yep, yep.

Dr. Weyand: Is the immune system exhausted, and that leads to cardiovascular disease, because good inflammation is failing? It also leads to a reduced antiviral immunity. Or, is the cardiovascular disease exhausting the immune system, so that these individuals no longer are capable of mobilizing immunity that protects them from infection and cancer?

Dr. Friedman: So tell me, what can we do now with these new insights of atherosclerosis as an immune-mediated disease, on a therapeutic front?

Dr. Weyand: I would say, we have taken first steps, we know from the CANTOS trial that blocking cytokines can prevent cardiovascular events. We know that the use of colchicine can be beneficial in a number of clinical scenarios. Now, colchicine does nothing else than inhibiting the inflammasome. This is a pro-inflammatory pathway that is explicitly important in microphages. And so, we know that patients can benefit when we stop exuberant inflammasome activation with colchicine. I think the holy grail is, can we make the immune system better? Can we not just stop something from happening, but can we make it better? Can we rejuvenate it? Can we maintain adaptive immunity? Can we utilize metabolic interference? If the immune system does indeed sense it's metabolic conditions, then we should be able to utilize that signal to educate the immune system to do the right thing. I think that's kind of the thinking now, can we interfere with receptor ligand pairs that lead to immune exhaustion, and by doing so lead to immune system improvement? Can we manipulate the biofuel utilization, the uptake, how these

cells metabolize the energy carrier that they take up? Because their eating behaviors seems to determine their functional behavior. So if we can feed 'em the right thing, they may do the right thing. So that's kind of the idea of pushing forward.

Dr. Friedman: I love it.

Dr. Weyand: And I think in one respect, we can probably, and we have already made progress, because it's obviously that with the prolongation of life expectancy, we have improved the conditions of the immune system into the eighties and into the nineties. So we want to prevent immune exhaustion, that means hyperstimulating the immune system is probably not a good strategy. And we are born with a certain capacity of the immune system, we want to stretch that capacity as long as we can. So infections that we do not get is probably a good thing for us. Preserve the reserve.

Dr. Friedman: Yeah, no, that makes a lot of sense. Well, Dr. Cornelia Weyand, thank you for a fascinating discussion. As a cardiologist, the thoughts of new approaches to treating atherosclerosis and coronary disease is terribly exciting. But it's so much more than that, it's atrial fibrillation, it's heart failure with preserved ejection fraction, and ultimately, it may lead to added longevity, it really is so terribly important. So, really appreciate both the work you're doing, and taking the time to share it with all of us, so thank you.

Dr. Weyand: Thank you so much.

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