ILSI 2021 Annual Symposium Session 8: COVID-19: Nutritional Vulnerabilities and Food Supply Challenges

Transcript of the presentation, Aging and immunity, Tamas Fülöp, PhD, University of Sherbrooke, Canada

So, of course, this is a huge comment to speak on aging and immunity, but I will try to make a sort of overview of what's going on in immunity and aging. And thank you, Professor Calder for setting the stage to explain how immunity works. So, it will make my task easier. So, the next slide, please. So, this is my disclosure. The next slide please. These are the abbreviations. So, if you get the slides, so you can refer to that.

Next slide, please. So aging is meaning time. So, you can see here, the lady who was the most aged, oldest person in the world, who is Jeanne Calment, who was about 122, which is considered actually is the maximum lifespan of human beings. And you can see that once she was young, middle-aged, and elderly. So, when we are speaking on older subjects, we should really consider, as already mentioned by Professor Calder, that the immunological history, what we can call actually after Professor Franceschi, the immunobiography is very important. Of course, as we have seen many other factors are influencing the immune system, but this is one of the most important when we are looking on the effect of aging to the immune system. The next slide, please.

The next slide, please. So, I wanted to make the set the stage that immune system is part of your huge other system, which is aging. Aging is a very complex system determined by external and internal factors, and they are interacting at different levels from the molecular to the organism level. So, there are interactions, there are feedback, there are many controls, which are in movement when you consider what is aging. And the immune system is part of this very complex system and determined by every other systems which are present and determine how we will age. The next slide, please.

There was a very big step forward when the group of Lopez-Otin in some years ago determined the nine hallmarks of aging. And this was a conceptualization to make really evident what is the main processes inside of our organism, which can define how aging is occurring with time. So, you can see many of that, and you have of course the deregulated nutrient sensing, so as we have heard before, so it's very important. But there are many others, like for the metabolism, the cellular senescence, the stem cell exhaustion, loss of proteostasis, epigenetic alterations, telomere attrition, genomic instability, and finally what we call the altered intercellular communication. Next slide please.

So inside of these nine hallmarks, and inside of this intercellular communication, you can see beside the neuroendocrine dysfunction and bystander effects two words, which is immunosenescence and inflammaging. And so, you can understand that immunity and the part of the immune changes with aging are part of the aging process, and from the nine hallmarks of aging. Next side, please.

So, this is from 2013, when the group of Goronzy just summarized very clearly, what's going on in the immune system with aging. And also, he contributed to the understanding of the adaptive part of the immune system, but things are progressing, and our thinking is evaluating. And you can see here that this was, and this is still sometimes the concept, that what we see in aging in the immune system is a sort of immune deficiency. So, I will try also to show you that beside having some decrease in the immune system, we have also other processes which can make our immune system stronger when we age. And of course, you have the inflammatory processes as we age, much higher in case of older subjects. The next slide, please.

So, what is immunosenescence? Next slide, please.

So, as we have heard, the immune system has two main major parts, which is the innate immune system, which is a standard for every multi-cellular living organism. And we have the adaptive immune system, which started very late in the evolution of the beings and the animals on the earth. So, the innate immune system is very ancient, which can react with almost everything that we have outside of our organism, and also inside of our organism. So, this is reacting to the pattern molecular, the conserved pattern, and also to the damage associated molecular patterns. So, every viruses, bacteria, or fungi that we have can react and find... When they are in... Innate immune system... Can see here, they really... For an inflammation... That this is... Eliminate invaders. And in most cases, this immune system is sufficient to eliminate the invaders, but it is not... The system... Of the aggression.

So, this is composed of cells, neutrophils, macrophages, dendritic cells and NK cells, can release by [inaudible 00:07:22] outside or inside of cells, and can have [inaudible 00:07:29] produced. And here, that the specific simulations of the major functions of these cells are decreased with aging. Mainly the chemotaxis, phagocytosis, the intracellular killing of bacteria, or even viruses, and also the production of various mediators which can eliminate out of these cells, these aggressions. The next slide, please. So, the... The next slide, please.

So, the paradox of the aging of the innate immune system, purpose of the pattern recognition receptors, that in the... No, come back, please. Sorry. So, this is constitutive... That's it. The constitutive activation of the system at the KSM state. So, which means that these cells and the increase of these mediators will sign a sort of hyperactivation state with time in elderly or older subjects. But when it's time to react clearly to a specific aggression, the specific activation is decreased. This is not meant that all the subjects cannot fight infections, but this means that efficiency of this may be decreased. And this is because we have all these external and internal stimulations constantly, and this maintain the readiness, or the alertness, of the innate system with aging better at the basal state than when they meet specific aggressions. The next slide, please.

This is to show, up at the red arrow, that in case of elderly subjects, already many signaling molecules inside of the neutrophils are in an activated, which means phosphorylated state. And when you try to stimulate specifically these cells, you have a decrease in this phosphorylation. This was our work; it was published some years ago. And the next slide will show the same from the group of Professor Janet Lord from Birmingham, where they show exactly the same. Then once you have the basic activation of these cells, which impacts the functioning of these cells, you cannot further stimulate these cells. So, this is a very important observation for the innate immune system with aging, the higher activation at the present state and the less activation during activation and specific stimulation. The next slide, please.

The one other very important task and function of the innate immune system, as already mentioned also by Professor Calder, is the antigen presentation. This is absolutely fundamental for good functioning of the adaptive immune system. This is just to show you that we can have presentation by mature dendritic cells, by macrophages, follicular dendritic cells. And these have a very specific task there, to all the specification and the activation of the adaptive immune system through the CD4+ T-cells, CD8+ T-cells, and the B cells. And their counterpart in this are these naive T-cells, CD4+ and CD8+ cells. And when we have problems in this antigen presentation, as we have in this aging, which means that the processing of the antigens is decreased, and also the presentation through the MEC2 or the MEC1 epitopes for these antigens is decreasing. There are problems for priming the adaptive immune system to work properly after an infection or an aggression. The next slide, please.

So, there are changes in the adaptive part of the immune system. There are phenotypic changes and there are functionality changes. We'll see first the phenotypic changes, which are very much studied by thousands of publications and many groups. And what is the consensus that there is decrease of the naive T-cells, with the loss of their possibility to have diversity at the TCR level. And there is, in the same time, an increase in TCR oligoclonality, which are meant to one antigen, and also a very big increase in the effector memory T-cells, with a loss of the CD28+ on that surface. So, the next slide, please.

So, you can see here at the cellular level, there are changes in the B cell compartment on the left, and you have in the T-cell compartment on the right the same changes. That the decrease with age of the naive B and T-cells, the increase in the memory T-cells, and also the increase inside of these memory T-cells of the exhausted and senescent T-cells, as we will see later. And in the case of B cells, we have also an alteration in the immunoglobulin specificity in the isotype and at the idiotype level. So, this immunoglobulin switch to perfect and adapted immunoglobulin, IgG production, is altered with aging. The next slide, please.

So, there are many questions actually still to determine what is the role of the cytomegalovirus. Many persons think that the cytomegalovirus is one of the initiators and maintenance for these changes with aging. But most of the time we know that there are changes which are caused by CMV latent infection, with the reactivation time to time, and also with the aging process. So actually, we know that CMV may contribute in some individuals, but most of the time, the aging of the immune system is independent from the CMV infection. The next slide, please.

So, there are four groups of the T-cells, which are the naive T-cells, the central memory T-cells, which keep some of the aspect of the naive T-cells. The effector memory T-cells, and the terminally differentiated memory T-cells expressing the phenotype. So, you can see here that with aging, we have a shift from the naive T-cells to all the effector memory and the TEMRA cells, which has very specific phenotypic expression, and corresponding to different functionality. The next slide, please.

So, when we see how naive T-cells can evaluate when they are stimulated with a specific antigen, and coming memory T-cells, you can see here that with aging, we have an increase in the TEMRA, which can express some NK features. So, they become more innate than adaptive. You have what we call the exhausted T-cells, as we will see later, and also, we have short-lived effector T-cells, which are increased. But in the meantime, the stem-like memory T-cells, which keep some of the possibility to divide as naive T-cells, are decreased, and also the functional tissue resident memory T-cells are decreased, which means that we have many cells which can have effector functions. But these effector functions are less efficient than in the case of a younger subject, because all the network of these memory T-cells are changing in their composition. The next slide, please.

So, when we consider the functionality, the most important functionality is the oligoclonal proliferation, which is decreased with aging. This is because the IL2 secretion is decreased, but also because the CD28 receptor at the surface of the T-cells is decreasing. In the meantime, you have the decrease in the telomere lengths and the telomerase induction is also decreased. And concomitantly, the damage to the DNA is increased. The next slide, please.

So, you can see here very schematically, the differences between the inducing of the functionality of these T-cells through the membrane and the receptors on the surface of the T-cell, and also the intracellular pathways, signaling pathways, which are altered with aging. So, in the young we have a feed forward mechanism, which is much higher than the feed backwards, but in the elderly, unfortunately, these cells are under inhibitory control, which means that even if they are stimulated, they have phosphatases. They have blunting in their different intracellular signaling molecules, which make them less responsive to specific antigens, which are coming from outside or inside, and presented by the antigen presenting cells. And you can see here that there are changes in the AKT/mTOR pathway, which is very important for the immunometabolism, and also for the maintenance of the balance between the metabolism needed as aerobic glycolysis or the ox-phos metabolism during the stimulation and the differentiation of these T-cells under antigen presentation. And you can see also here, the changes in the chromatin, and also the epigenetic changes that we will discuss later. The next slide, please.

So, you can see here, as it was presented and shown for the innate immune system, the present hyperactivation in the present state, you have the same from the Shen-Orr group, which was presented also in T-cells, that mainly the pSTAT molecules were also, which are the intercellular pathway for cytokines to transmit the signals from the outside to the nucleus. They are also in an activated state in T-cells of older subjects. The next slide, please.

So, as you can see here, very briefly that the epigenetic changes mainly at the histone methylation, the histone changes by methylation acetylation. So, the histone modification, and also the DNA methylation will really determine which part and how the DNA will be transcribed. These are transcriptional regulator of the DNA. So, the next slide, please.

We can see that beside all the changes that we have at the level of the DNA transcription and the epigenome modification and control, we have a global hypomethylation, and also the heterochromatin, which is less transcribed, is lost, and there is a redistribution. So, the restriction and the inhibition is less, and the activation is much higher with aging in these T-cells, through the development of naive T-cells towards the differentiated and very differentiated states of memory T-cells. The next slide, please.

So, one of the major underlining cause of these changes besides the post-translational changes is the involution of the thymus. The thymus is starting to involute very early after the puberty, and almost not existing at 60, when we attain this age. And this makes changes in the production and the priming of the T-cells. So, which you can see on the right side, that the naive T-cells are decreased with aging, because there is changes in the epithelia and in the hormonal level in the thymus. But in the meantime, you have an increase in the self-reactive T-cells and also in T-regs, which are really increasing the possibility of autoimmune diseases, and also negative control on these self-reactive T-cells. So, this is leading to what we call the inflammaging. The next slide, please.

So, the conclusion from this first part is that elderly are immunoremodeled with fewer naive T-cells and dysfunctional T-cells, due to chronic antigenic stress and thymic involution, which is coupled with innate immune response, resulting in what we call the inflammaging. Next slide, please.

So, we will look, what is inflammaging and what are the sources which led to that. So, we already saw that one of the main reasons of this inflammaging is the disbalance between the innate and adaptive part of the aging of the immune system. When the hyperactivation of the innate immune system out-compete the changes, what occurs in the adaptive part of the immune system. And this was the base... the next slide, please... of the conception by Franceschi in 2000 of this inflammaging concept. Because of this chronic antigenic stress and oxidative stress, which arise each day in our organism and accentuated by the aging of the organism, and the stimulation by tumor antigens, beta-amyloid, oxidized LDL/AGE products, and others, stimulation by the persistent viral infections that we have through our life, with HSV1, with the Varicella-Zoster, the CMV, which leads to the changes that I have shown you before. The next slide, please.

So, this is interesting, that the inflammaging and even aging is an evolutionary and predicted byproduct of the degeneracy of damaged sensors, which means that with aging, we have more and more sense for the molecules, which are stimulating our system. And there are really a limited number of evolutionary selected promiscuous sensors to all these numerous stressors, and which is mainly are on the macrophages, which mean that the inflammation is really macrophage centered. But as you can see, the inflammaging and the fan out of this huge number of stressors and less sensors is there are even less molecules which can be the effector of this inflammaging, namely pro-inflammatory cytokines. The next slide, please.

So, one of the stimulants of this process is what we call the circulating mitochondrial DNA. Not only the circulating, but also the intracellular mitochondrial DNA, as we know, actually, can be one of the powerful stimulant of this inflammaging. So, we don't need all these from outside, infections or other triggers, but from the inside, we have already quite a lot of changes, which can fuel what we call inflammaging. The next slide, please.

So, you can see here how the mitochondrial DNA can lead through the inside TLR receptors, which are the TLRs three, seven, nine, to the activation of the NF-kappa B inflammatory pathway, and also by stimulating what we call the inflammasome and resulting in increased pro-inflammatory cytokines. The next slide, please.

It should be also mentioned that this mitochondrial DNA is also very important to stimulating what we call the mitochondrial antiviral signaling protein, which is really important to stimulate and put into movement the intracellular pathways to produce two very important antiviral cytokines. Which are the type one interferon, which are stimulated also in the meantime by the mitochondrial DNA, through the cGAS-STING pathway, which is very important for the cellular defense against viruses. The next slide, please.

So, we have seen the nucleic acid, how it can fuel the inflammaging. We'll go to the two other part, which is cellular senescence and the gut microbiota, very briefly. The next slide, please.

So, one of the major advances in aging and also in immunity in aging since the Hayflick theory, which was the replicative senescence, that we could really sense how these senescent cells can increase with aging, and also fill the tissues. And even if they are not capable to divide, they are still there. And they

are metabolically extremely active, because they can be stimulated via these different pattern recognition receptors. And they become what we call the senescence associated secretory phenotype. And this means that these cells, which attain a certain limit of their proliferation capacity, become resistant to apoptosis and fill the tissues, and the space, and fuel the inflammaging by their inflammatory products. The next slide, please.

And these cells should be distinguished, and this is a big debate in the immunity on aging, whether the T cell exhaustion is the same than the T-cell senescence. What are really the proportion of these cells? And this is extremely important when we think about the treatment of diseases and the treatment capacity that we have with the checkpoint inhibitors, that the T-cell exhaustion can be reverted, and they become functional, but the senescent T-cells are not able to be activated or be really useful for the organism, and they should be eliminated. So, the next slide, please.

So, this is to show that and reveal here on that, and was also mentioned that a good microbiota, eubiosis is very important for the efficient and really good working immune system. This is just to show you how the interaction between the barrier and the cells, and the different component of the microbiota can direct and influence the immune system. The next slide.

With aging, of course, we have many changes in the microbiota, which doesn't mean that it's pathological, because there are increase in some type of component species of the bacteria which compose the microbiota, and also, they are decreased or increased. So, there are various changes, but nevertheless, these changes can influence the changes in the whole immune system with aging. What is interesting? The next slide, please.

That the microbiota in very older, in the extreme longevity, in the semi-supercentenarians is completely different from elderly subjects. So, we know that in the blue zones where there is an increase of these extreme longevity persons, the semi-supercentenarians, they have a completely different microbiota, even from young or elderly between 65 and 75. And we know that even they are different, they are more close to what the young persons can present than the elderly. Which means that many factors that we have heard in nutrition and lifestyle can influence, and with the genetic background can maintain a microbiota which can sustain a normal immune response. The next slide, please.

So, this is to show how the different nutrients and diet can influence how the microbiota can have the modulation of the immune system. And the Mediterranean diet is mainly maintaining immune tolerance, and good immune functioning. And mostly the Western diet is their components may lead to what we call the inflammation, and also influence the inflammaging. The next slide, please.

So, all together, the senescent cell hyperfunction, and also the innate immune hyperfunction are leading to organ damage, age-related diseases, and finally death. I will just mention briefly one or two diseases where this is important. Next slide, please.

We cannot, we have heard also on COVID-19, and we know that impact more in the severity and also for deaths, the elderly subjects, which is shown here. The next slide please.

And many things with the aging process inside of the immune system can influence the susceptibility of the elderly subjects to the COVID-19. And you can see here, the uncontrolled immune response, the epigenetic dysregulation, immunosenescence, inflammaging, the biological age, which is higher than the

chronological age. And of course, environmental factors and comorbidities will influence the susceptibility. The next slide, please.

This is a busy slide, but just to mention that the decrease in the naive T-cells, which aging, that you can see on the right side even in CD4+ or CD8+ T-cells, may highly influence the response and the susceptibility of elderly subjects toward COVID-19. The next slide.

And not only the decrease in the naive T-cells, but the incoordination, which is appearing with aging, between the different part of the adaptive immune system, namely the production of neutralizing antibodies against the S protein and also the effector functions of the CD4+ and CD8+ T-cells as the memory formation should be made in a real, coordinated way towards a viral infection. And even more importantly, towards the COVID-19, the SARS-CoV-2 infection, which means that in the lower part of the slide, you can see that there is a complete incoordination between the production of antibodies and the function of the T-cells. The next slide.

Why it is so also, because there is a preponderance of the macrophages and monocytes in the subject, old subjects, infected with SARS-CoV-2 too. And you can see where you have the arrow that compared to a young healthy and aged healthy subject, aged people who has the COVID has a higher monocyte activation and higher monocyte number. And also, when you compare young COVID and aged COVID patients, you can see that there is an imbalance between the cellular compartment of the immune system. And we have a hyperactivated immune state that you can see on the bottom part of the slide, with the expression of the genes, which are related to the hyperactivation inside of the inmate system. So, which means that one of the most important susceptibility to COVID-19 in the elderly is the hyperactivation of the innate immune system, which could exist before the infection by this virus. The next slide, please.

So, these are all the components which can determine why elderly has a higher susceptibility towards the COVID 19. The next slide, please.

So, one very important disease of the elderly is Alzheimer's disease. And you can see, and nowadays this is well accepted, and it took perhaps 30 years to develop and to link the Alzheimer's disease to the neuroinflammation. And this is neuroinflammation, which makes after the lifelong stimulation of the neuroprotective microglia to neurotoxic microglia and being part of what we call the inflammaging process and destroying at the end of the road the cholinergic neurons and leading to these very important neurodegenerative diseases. So, it is a very quick overview, but this is part of what I told you on the changes in the immune system with aging. The next slide.

This is to show you that about 30 years before the clinical manifestations of the Alzheimer's disease, you have all this chronic antigenic stimulation, either by beta-amyloid or by infections, which leads to what we call now the neuroinflammation. And once the aging of the microglia is manifest, you can have the clinical manifestations of the Alzheimer's disease. The next slide, please.

This is to show that the same is happening in cancer with all the outside/inside stimulant stressors during the lifetime of the individuals. The next slide, please.

So, this is to mention that during these last years, we have what we call the innate immunity, which has now what we call the trained innate memory, which means that each time that you stimulate the immune system and the inmate immune system especially, there are changes in the

immunometabolism and in the epigenome control, which makes these cells more sensitive. And when you have following and repetitive infections, or aggressions, you can have a higher response. So, this is a nonspecific memory, but this makes the organism much more ready to answer to a second served challenge that was the first one. Of course, we should mention that this is not only a positive way to control infections, but can be also, as we see sometimes in aging, could lead to what we call the immune paralysis, and not response anymore, and making more inflammatory molecules for destruction inside of the organism then the destruction of the aggressors. The next slide, please.

This is to show you how the epigenetic changes inside of the monocyte macrophages and NK cells possessing that trained innate immunity can control finally, the higher response when a new aggression is occurring inside of the organism. So, we think that the inflammaging is a sort of mirror of what's going on in the trained innate immunity, at the innate immune level. The next slide, please.

So, this is to show you that after a hip fracture, there are still production of TNF-alpha. Okay. Shortly I will finish. Yes, the next slide, please.

This is the geroscience, the geroscience... the next slide, please... geroscience is stating that the inflammaging is incorporated more clearly inside of the nine hallmarks of the aging process. And this means that... the next slide, please... all the different processes inside of the aging and including the inflammaging are the common root for all the age-related diseases. So, if we can really impact these processes, diseases related to aging will be mitigated. The next slide, please.

They don't really take into account that the inflammaging is balanced by the anti-inflammaging. And this means that at the same time that we have an inflammation we have also anti-inflammatory control, and you can see that the balance between inflammation and the anti-inflammation can lead either to age-related diseases or frailty, or to successful aging or longevity. The next slide, please.

So, this is conceptualized in this way of aging that there are three types of aging, which is the one is a pathological, the normal, or the successful. And this is mirrored by what we can see inside of the immune system. The next slide, please.

So, this is the comparison of the three types of immune trajectories, which are leading and communicating with each other. The geroscience straight link from aging-related diseases, the Franceschi conceptualization with the differential trajectories, which are modulated by the outside and inside factors, and the interrelation between the aging and the age-related diseases. The next slide. The next slide, please.

So, this is the new paradigm of the dynamic immune changes with aging. That immune changes are not all detrimental, but these are part of the adaptive immunity that make the older organism sometimes more efficient, but the adaptation can be maladaptation. Then we have all these different diseases. The next slide, please. The next slide. Next slide.

This is the summary and the perspective. So, the immunosenescence should be considered as a remodeling adaptation of the innate and adaptive immune system in function of chronic aggressions and time. It is necessary process of adaptation, but detrimental for responses to new, for example, cancer antigens, or viral antigens. The intricate relationship between immunosenescence and inflammaging induces a vicious cycle of self-maintenance, which may result in maladaptation. Elderly in the clinical setting are doing much better than conceptualized from experiments. Real deep human

longitudinal studies are needed. And the anti-inflammaging process targets the changing immune system of the elderly to contain inflammaging at an acceptable level. Thank you for your attention.