Biogerontology **4:** 329–334, 2003.

Interview

Continuous remodeling as a key to aging and survival: an interview with Claudio Franceschi

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I have been fascinated and impressed by Claudio Franceschi, both as a person and as a scientist, ever since I first met him about 15 years ago. That was the time when the Molecular Biology of Aging group was initiated within the framework of EURAGE, and several new research laboratories were getting involved in the nascent field of molecular gerontology. With his lively and fully expressive Italian body-language, his imaginative ideas, and his extensive knowledge of a wide range of subjects, Claudio impresses everyone. I have found him to be extremely encouraging, tolerant and especially helpful towards young students. He has been instrumental in starting up and spearheading the 'centenarian research programme' in Italy, establishing the health criteria, immunological parameters and gene associations in people with exceptional longevity. At present, Dr Claudio Franceschi is a Professor of Immunology at the University of Bologna and is also the Director of the Italian National Research Institute on Aging.

In my continuing series of interviews with pioneers of biogerontology, Claudio has been an obvious candidate. The opportunity for making an interview with him came during the 3rd International Conference of Biogerontology, held in November 2002, at Montecatini Terme, a small town near Florence, famous for its hydrotherapy anti-aging clinics. Since almost all the anti-aging centers were closed for the winter, therefore, instead of having a conversation while relaxing in some hot water bath, Claudio and I ended up sitting on a rain-drenched and very cold wooden bench in a public garden near the conference venue, where I asked him:

SR: How and why did you get involve in research on aging?

CF: Well, it was purely by chance that I came into the field of aging from immunology which is a highly advanced and sophisticated field. Between 1975 and 1980, when I was an Assistant Professor of Pathology at Bologna, I was studying immunodeficiency-related problems in children and somebody sent me a blood sample of a Down's syndrome patient to be used as a control. But there were many problems with that sample, and we realized that Down's syndrome was actually a model of accelerated aging. So I started checking the samples from elderly people, and one of the first papers that I published in 1981 was about DNA repair in the lymphocytes from the old people. Then by the end of 1980s and early 1990s I realized that it may be more interesting to study longevity instead of aging. I was attracted by the idea of studying exceptional individuals with a long lifespan. Since I was trained originally as a pathologist and an immunologist . . .

I interrupted Claudio to know a little bit more about his early education and training.

CF: I got most of my education and training in Bologna, though I was born in a small city, Frosinone, close to Rome, where my father was working for an insurance company. When I was about thirteen years old, my father moved north to Modena, and later on for my university education I went to Bologna. For five years I also got the chair of immunology at Padova, which is one of the best universities in Italy. From there I returned to Modena, and now since 1998 I have been in Bologna, sort of completing the circle.

Back to the question of aging and longevity . . . .

CF: I thought that this popular idea in medicine, that very rare diseases can be a useful model system to understand what is normal, could also be applied to people with exceptional longevity in an opposite manner. Centenarians or very old people should have certain biological advantages or characteristics that allow them to live much longer than most of the other people in their group. Although lifespan is a continuum, extreme phenotypes are also very interesting. So, we decided to look into the immunological status of centenarians. At that time the idea was that everything should decline with age, and that is what we were expecting to find. But we were surprised to see that whereas some parameters were declining, others were actually increasing in centenarians. For example, we observed that NK lymphocytes were really well preserved in these individuals. Even within T-cell populations, there were some subpopulations which were decreasing in number whereas some other subsets were increasing in number. It was the same story for B lymphocytes. It was totally unexpected and contrary to what was generally known in the field of aging, specially with respect to various physiological functions. That gave rise to the idea of continuous remodeling, that aging is not just an accumulation of damage or loss of maintenance and repair; rather the body is continuously going through a process of adaptation. But, this idea is still not taken into consideration by some researchers.

Continuous remodeling and shrinking immunological space

I wanted Claudio to develop on the topic of adaptation, and so I asked him to explain: the body adapts for what and in what way could it do so?

CF: Adaptation to damages, and the optimization of the resources which are still there. So, this is a very dynamic process which is not simply repair of the damage, but repair plus something else. It is a very dynamic situation and the direction of events and changes can be very different from what you would normally expect from aging as a 'progressive decline' idea. The body is adapting for maintaining the homeostasis. The immune system is a very clear-cut example. It is now known that the major change in the immune system with age is the accumulation of memory and the shrinking of the immunological space. Aging is the fact of the normal functionality of the body. When you are exposed to an antigen, your immune system is made to react and create memory cells. If you continue to do this physiological act for more than fifty or sixty years, your immunological space is filled up with memory cells. This is an example showing that aging is a consequence of normal physiological processes and reactions against stress. So, adaptation is the key rule for our survival.

SR: How long does it take to completely fill the immunological space?

CF: Well, for human beings it appears that there is enough immunological space probably for about fifty years or so, which is our natural lifespan. But the rate of filling of this space will depend upon how much and how frequently an individual has been exposed to antigens, and how often it has been challenged immunologically. If you live in non-hygienic conditions, for example in economically poorer countries, then your body is being continuously challenged and the immunological space is filled up much earlier than in people living in much cleaner and hygienic conditions.

SR: But it can be other way around too; if you live in too hygienic conditions, then the body has a much weaker defense capacity!

CF: Yes, that is true. It should neither be too much cleanliness nor too much exposure. But the fact is that with aging there is a shift towards memory state and the new challenges cannot be met properly. I think something similar must be happening in other systems also, and so the immune system can be a paradigm for the general physiological alterations with age. In the brain too, you do not lose everything, and instead there is remodeling occurring there. So, you see, the remodeling idea is a very general idea and not just limited to the immune system. In my view, aging is a continuous remodeling in every organ, every tissue, everywhere.

SR: This idea of continuous remodeling fits the idea of homeodynamics better than the old term homeostasis, because in homeodynamics the concept of what is normal is also changing all the time . . .

CF: Exactly! For example, what we call the normal range of cholesterol at one age may not be directly applicable at another age. This has far-reaching implication for establishing clinical parameters, especially in old people where it may be quite normal to have other levels.

Differences in lifespan and immunological noise

SR: What about the rates of aging in different species?

CF: Yes, that is very important. It looks like basically everything is very well conserved in evolution. Major metabolic pathways, genetic information transfer, signal transduction and so on, everything is highly conserved. So, how can you understand major differences between species, lifespan? I think that small changes in only a few important key pathways can have big effects on longevity. The basic ideas coming from the study of the complex networks show that there is a hierarchy, and some nodes in the pathways are more important than others because they are related to more other pathways. Thus, there may be a few key genes which can be altered and big effects on aging and longevity can be seen. In this context remodeling is adjusting something that is basically conserved.

SR: Do you mean it is a kind of fine tuning?

CF: Exactly, that is fine tuning. This is the reason that people have been so successful in experimentally increasing the lifespan by changing this or that. Remember that we are very complex systems, and so even very small differences in certain key elements can have very large effects at a distance at some other level and in the long run. Otherwise you cannot have this scenario of extremely wide variation in lifespans when almost everything is conserved at biochemical and fundamental level. Differences in metabolic rates would be very important in that respect . . .

At this point, we were interrupted by the sudden arrival of two Italian gentlemen who wanted to show Claudio some papers and books, and for about 10 minutes Claudio talked with them. That also gave us a chance to straighten our legs and realize that we had been sitting on a very cold bench, which had almost numbed us. After the guests had left, Claudio told me about his collaborative work with them, where he is developing a set of immunological tests and biomarkers to be applied to the elderly in order to keep track of their health status. I wanted to know more about the usefulness of such biomarkers . . .

CF: These immunological biomarkers are so strong that they have helped us to develop certain mathematical models which have predictive powers. What is even better is that they have allowed us to understand the mortality curves in the last two centuries. Assuming that the immunological burden was much larger in the past than in the last fifty years or so, the equation of this model fits much better on mortality curves starting fifty years ago. This means that the attrition of the immune system in the past was so strong that the real immunosenescence did not occur, and people were dying much earlier due to other reasons. Thus immunosenescence did not play a large role in aging and longevity in the past, but now when we are living in a much cleaner environment, the importance of immunosenescence is even higher. Previously, it was the immuno-failure or the collapse of the immune system due to the heavy load of infections or other antigens which was causing the death of an individual. But now, immuno-senescence is playing a major role in morbidity and mortality because it is related to inflammation and is a driving force behind major age-related diseases.

SR: I like your distinction between immuno-failure or immuno-collapse in the past and the immuno-senescence at present as the cause of death . . .

CF: We also use a term 'inflammaging' for this chronic inflammation and stress which may be the basis of several age-related pathologies, such as atherosclerosis, neurodegeneration, diabetes and others. All these diseases have a chronic inflammation component to them. That also explains why the drugs that are used against high blood pressure are also very effective against diabetes, and the drugs that have been used against diabetes have been found to be quite effective against Alzheimer. All these diseases are related to continuous stress, which is also the cause of inflammaging.

SR: In other words, is inflammaging the failed adaptation?

CF: No, no. You have to start with the concept of Metchnikov, the great Russian scientist. More than a hundred years ago, Metchnikov suggested that inflammation is a physiological defense mechanism. But a continuous use and overuse of this tool during a lifetime leads to inflammaging, which is the result of the body's normal physiological response to damaging agents.

SR: But it sounds like the old wear and tear theory! Since the body is using a system, finally it is worn down. Is it just a passive wear and tear?

CF: No, no, to the contrary. It is the result of active physiological responses to neutralize damaging agents.

SR: But isn't it still a question of use or overuse. If we don't use it, perhaps we live longer?

CF: No, if you don't use it, you die very early on. But if you use it continuously, you pay the price later on.

SR: Can we then regulate these responses to eliminate aging or to live for ever?

CF: Not living for ever, no, no. But the key genes involved in these physiological responses, which are highly conserved during evolution, may possibly be modulated. If you study the evolution of the immune system from invertebrates to man, what emerges is that the macrophage is the central cell throughout the evolution, and the basic mechanism of stress response and macrophage activation are extremely well conserved. So within this conservative scenario, if you want to make big changes in survival, you just need to make small changes in the few key nodules in the hierarchy. With the system biology approach, we should be able to identify them, and making changes in them will have big effects on survival.

SR: Survival for ever?

CF: No, we also have to consider stochasticity, which means the enormous noise in the biological systems. For example, the specificity of the immune system emerges within enormous noise and degeneration. But the noise is extremely important for having the response. We are now working on the hypothesis that immunological noise is important for having the secondary response.

SR: What is this notion of immunological noise?

CF: Immunological noise is that the immune system is continuously exposed to antigenic challenge which is below the threshold of inducing immunological response. Contrary to the information theory, according to which the noise must be reduced to have a response, the immune system requires this noise to manifest response. Probably this is true of the whole body. If the noise is too low, the body is non-responsive, but if the noise is too high, it is no good for the body. I would also say that different species have set different levels of noise for their survival and longevity. So, this noise is the one which brings in the element of stochasticity and also explains the impossibility of living for ever.

SR: Do you think modern biologists are now accepting these ideas of stochasticity and randomness and are coming out of their gene-determined views?

CF: I think we are schizophrenic nowadays. On the one hand, we are focused on single genes, but we are also beginning to realize that we need to make use of what physicists and those who are studying complex systems have been doing. They have made tremendous advances in understanding and developing new ideas.

Powerful tools, poor conceptualization

CF: Biogerontologists are a little bit behind. They are still stuck too much in genetic ideas. Until now, we have been looking at individual genes, but genes work together and in interaction. This is why we have so much difficulty in interpreting gene expression array data where hundreds of genes are going up and down. We have no clear conceptualization about how different genes and different gene pathways may interact. We have very powerful tools, but very poor conceptualization.

SR: What may be the reason for that?

CF: Well, the reason is the way we have been trained. For example, I was trained first as a pathologist and some others have been trained as molecular biologists, very much focused on single genes, and we remain focused on that. I started an inter-departmental center in Bologna with physicists, mathematicians, informatics, biologists and so on, but it was difficult to understand each other. The funding agencies also do not like to support such kind of centers, and it is difficult to publish many papers from such activities. But, I think biogerontologists can really benefit from these kind of interactions. We need to train young students in a wide range of subjects and not just limit them to one or two specific ones. A classic example of cross-fertilization is what we are doing these days, which is having genetic data about the elderly and the centenarians but analyzing it from the view point of demographers.

SR: What about intervention research? Are there any interesting developments happening?

CF: Most of the intervention research is commercially driven and is often limited to cosmetic applications. We are trying to find ways to rejuvenate the immune system.

SR: Sponsored by some companies?

CF: No, no, I am not a company man. I am an old style academician, and in my perspective, making money out of science is not part of my education. I am trying to make academic companies in Italy, and we are trying to study the genetic component of the immune response. We want to make these tests useful for the clinics.

Influences and ideas

I wanted to know also about the personal life and influences that may have shaped Claudio Franceschi. So I asked if he could identify any events or any individuals who may have influenced his way of thinking and his work significantly?

CF: As I have mentioned before, I entered the field of aging through immunology. So, the people who influenced me more were from immunology, like the Australian Nobel Laureate Macfarlane Burnet. I was translating his book, 'Self and Not Self', in to Italian, and that probably had more influence on me than any other. Also, during my training as a pathologist, I was really influenced by the writings of Virchow. So, it was not people from the field of aging, but those working in immunology and pathology that had an influence on me. I also dedicated a couple of my papers to Metchnikov. He was really a giant figure in immunology, not only for demonstrating the significance of the innate immunity and macrophages, but he was also the first one to realize its importance for longer lifespan and survival. He was the first one to propose yogurt as an anti-aging treatment by decreasing the intestinal bacterial flora from where damaging chemicals go around in the body.

SR: I have always considered you as being a very different kind of scientist than others; do you also visualize yourself as being different?

CF: Yes, to some extent. First of all, I was trained in a secondary school 'licio' with an emphasis on humanities: Greek for five years, Latin for eight years, philosophy and other subjects in the academic tradition. When I decided to have my career in medicine, I first started in general pathology, which gave me a very general perspective on health and disease. I am very respectful to other people's ideas, and whatever I have done is due to a very good team of Italian scientists and students that I have over the years.

SR: What about recognition from other scientists? Do you think that you have got your fair share?

CF: On the whole, yes. But sometimes I think that some of the ideas that I have proposed have been considered to be more specific than they really are. Some concepts that I have developed have much broader implications than the immune system only. For example, I wrote a paper in 1989 about the importance of apoptosis in aging, at a time when nobody was thinking about it. This paper is not quoted as frequently as it perhaps deserves to be. Then there were some long held beliefs that I challenged, for example, about the maintenance of many immune parameters even in the centenarians. But I have no complaints. I am enjoying a lot, and this is the best period of my life.

SR: In addition to scientific research, what are your other interests?

CF: In sciences, I am very much interested in combining different fields, such as physics and mathematics, but starting from strong experimental data. Outside science, I would like to have more time for painting. But, I am very much involved in popularizing science. I have written for the Italian edition of the *Scientific American.* Almost every month I write in one or the other popular magazines about aging, about immunology and other topics. I think that this interface between science and the public is extremely important. Also, being the Director of the National Aging Institute is being a part of the political process about changing attitudes towards aging research. My wife is a Professor of English literature and my daughter is studying anthropology, and they are both studying aging in a broader perspective. So, in the family, we are developing a broader anthropological perspective to look at aging. My wife is studying aging from the woman's perspective and

cultural perspective, how the body has been looked at in different times in different cultures. What I would like to have time for is to study the philosophical implications of what I am studying, for example the idea of the self, which is an immunological concept, but it starts from philosophy. Immunologically, the self changes with age, but how does the perception of self changes with age. In the same way, the concept of body, its conceptualization in philosophy and in science, and how the body change with age. I have been teaching this to medical students in Bologna, and this is something totally new. This was a fantastic course, and students really liked it.

Science and religion

Finally, I wanted to know what he thought of mixing science and religion. The reason for asking that was that Italy is still a very religious country, and the influence of religion can be seen everywhere in daily life. Does and should religion influence scientific research, and is it possible to combine these very different ways of looking at the world without compromising either?

CF: Religion is very pervasive in Italy, but personally, I am not religious anymore. There is no direct influence of religion on science, but there is political influence. These days there is all that discussion about stem cell research and cloning, and also our kind of work on the genetics of aging will raise ethical questions. In the future, the religious background of Italy will emerge even more strongly and that will bring out more differences between Italy and other European countries. Until now, I was totally free in doing whatever scientific research I wanted to do. But it could happen in the future, and I hope that bioethical questions are discussed openly by the public. Specially in the case of biogerontology we are not prepared at all for the implications of life span prolongation and other issues. Even among scientists, there is no discussion about this.

SR: How should we prepare for that?

CF: Well, for example, by having special lectures and sessions on bioethics and related issues in aging meetings like this. There is no question that we need to go very deep in our field, but we also need a much broader approach in our thinking and in our experimentation. It is really a big challenge; you have to be up to date in molecular biology and its techniques but also be fully aware of other fields and other ways of approaching an issue. We also need that perspective at the clinical level while dealing with real people and their real problems. Even the concept of continuous remodeling needs to be applied at the patient level, and the body treated accordingly. For improving the quality of life in old age, we perhaps don't need more science, but we need to have correct application of a lot of knowledge that we already have.