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Senescence: the cost of being young and healthy?



Full text

The fitness of youth has to be paid for in later life by an increased incidence of age-associated diseases. Such a concept of "antagonistic pleiotropy" was defined by Georg Wick (Institute of Biomedical Ageing Research, Austrian Academy of Sciences, Innsbruck), who opened the immunosenescence session of the "4th Symposium on Cytokine and Apoptosis in the Cardiovascular System". This well-established argument runs as follows: genetic traits are only subject to the pressures of natural selection until reproduction is accomplished. Any genes conferring an advantage in early life will be selected for, regardless of whether or not they are damaging in later life. Thus, like an athlete on steroids,

peak performance early on is associated with serious problems later. Examples were presented illustrated with work from Pr. Wick's Institute, on some age-associated diseases such as Alzheimer's and atherosclerosis, where antagonistic pleiotropy may be at work. The most dramatic demonstration of this concept is arguably in defense against infectious disease. There must always be a measure of "overkill" in the immune system to ensure that infection is adequately dealt with, because in the wild, infections are the main threat to life (apart from starvation and predation, which of course each have their own unique evolutionary effects). There are convincing data suggesting that atherosclerosis is at least partly associated with autoimmunity caused by immunological cross-reactivity between microbial heat shock proteins and stress-induced endogenous heat shock proteins [1]. Indeed, atherosclerosis begins to develop from an early age, but the process proceeds so slowly that it becomes life-threatening only in the post-reproductive period. Hence, the necessity for defense against acute mortality due to infection is more important to the species than degenerative diseases in later life. This appealing view implies that natural selection pressure controlling life span is operating in younger individuals rather than in later life. But is this really true? Other hypotheses propose that longevity might have been selected for in humans (and possibly other social mammals), according to behavioural traits such as the "caregiver" hypothesis, or the "repository of group knowledge" hypothesis. Anyhow, it may not be so quixotic after all to search for longevity-promoting genes. Possible candidates are now beginning to come to light [2]. Clearly, knowledge of the nature and function of these genes may provide insights into anti-ageing interventions.

One area in which such longevity assurance genes may play an important role was discussed in detail by the second speaker of this session, Helle Bruunsgaard (Department of Infectious Diseases, Rijkshospitalet, University of Copenhagen), namely, in the control of inflammation. Many examples, which could also be interpreted according to the paradigm of antagonistic pleiotropy were given. It is becoming increasingly clear that a pro-inflammatory phenotype in the elderly, particularly elevations of plasma CRP, TNF- α and IL-6, is associated with increased morbidity and mortality. Reciprocally, an "anti-inflammatory" phenotype, especially regarding IL-10, may be associated with longevity. For example, a promoter polymorphism related to higher IL-10 production is associated with longevity in Sicilian women [3]. However, as mentioned earlier by G. Wick, the price paid by the majority of the population for low inflammation

earlier in life may well be a higher incidence of death from infection. As seen for many other parameters, what is poison for you when young, is good for you if you survive to an old age, e.g. high cholesterol levels [4]. Therefore, we should be searching for genes conferring resistance to these factors beneficial for later life but probably themselves exerting strong selective pressures earlier on, a reverse antagonistic or "agonistic" pleiotropy, as it were. Thus, longevity-assurance genes would turn out to be genes conferring resistance to insult in early life.

In my own presentation, I argued that T cell clonal exhaustion may contribute to the immune dysregulation seen with advancing age and that this can be modelled *in vitro* in T cell cultures. Changes in positive and negative costimulatory receptor expression on T cells, influenced by the cytokine environment (e.g. TNF- α downregulates CD28, an important positive costimulator) and themselves causing changes in the T cell cytokine secretion pattern (e.g. decreased IL-2 and increased IL-10 from the same clones as they age in culture), contribute to this state of affairs. Reduced average telomere lengths in many old T cells may be a possible cause of growth arrest, but because this is not universally observed in all old clones which nonetheless die, it seems unlikely to account for clonal exhaustion in itself. Data from our CD4⁺ T cell clones implicate oxidative DNA damage as the most likely cause of cell loss. Because these cells are rapidly dividing and are metabolically very active, this is not a surprising finding. The free-radical theory originally proposed by D. Harman and developed over many years since [5], suggests that much of the ageing process in general is caused by damage to DNA (and other molecules) induced by reactive superoxide radicals produced by mitochondria as part of normal metabolism. Longevity may be strongly influenced by the way in which organisms deal with the production and control of this process [6]. Preventing the accumulation of oxidative damage seen in the T cell clones might therefore extend their functional lifespan. Recently, the striking finding that the introduction of hTERT into human T cell clones commonly results in the "immortalisation" of the majority, may therefore imply that telomerase does not merely maintain telomere length, but may have other as yet undiscovered functions, for example, in DNA repair. An alternative possibility remains that growth arrest results from critical shortening of a small number or even just one single telomere; if the cell could not repair this in the absence of telomerase, growth arrest would occur despite maintenance of average telomere length. Nonetheless, in fibroblasts where this has been studied most, the onset of

replicative senescence was found to be significantly correlated with mean telomere length but, strikingly, not in chromosomes with the shortest telomere length [7].

Not all problems in immunosenescence are the result of cell loss. The above considerations may apply more to CD4 than to CD8 cells, because the former tend to become increasingly susceptible to apoptosis as they age, whereas the latter may become increasingly resistant. The problem with CD8 cells in the elderly may therefore be the opposite, namely, that they fail to undergo apoptosis and accumulate. The presence of oligoclonal expansions of CD8 cells from middle age in humans is well established. The nature and specificity of these cells has remained obscure until recently. Using tetramer technology, Qin Ouyang, in our laboratory, has shown that a large number of clonally-expanded CD8 cells in the elderly carry antigen receptors for *one single* immunodominant epitope of CMV, which is not seen in young controls. More than 10 % of all peripheral CD8 cells may carry this receptor, justifying the conclusion that the immune system in the very elderly is obsessed with CMV. However, sorting the tetramer-positive cells and testing their function by measuring antigen-specific IFN- γ production in ELISPOT, revealed that the fraction of functional cells in the elderly was far smaller than in the young. This accumulation of non-functional CMV-specific cells in the elderly may also contribute to what we have termed the "immunological risk phenotype, IRP", established as a predictor of residual longevity in longitudinal studies of the very old ([8], Ouyang *et al.*, this issue [39]). Whether this and other parameters of the IRP are clinically relevant in a practical sense remains a subject of debate [9].

Angelika Bierhaus from the University of Heidelberg, discussed the RAGE of AGE, that is, the receptor for advanced glycosylation end-products, rather than an expression of annoyance that scientists have not yet found a way to prevent companies from lying to their customers providing them with inefficient anti-ageing products. Indeed, AGEs accumulate in age and provide a chronic stimulus *via* RAGE, which activates the NF- κ B transcription factor and mediates effects similar to the chronic inflammation discussed above. Despite widespread expression of RAGE and extensive investigations in this field, little seems to be known about the "orphan" receptor RAGE: ligands include β -amyloid peptide, prions, amphotericin, S-100 and more, as well as AGEs. Possibly the development of RAGE-knockout mice will be informative in this respect. The final speaker of this session, Klaus Pfeffer (Institute of Medical Microbiology, Immunology and

Hygiene, Technical University of Munich) described several mouse KO models, which always seem to yield unexpected results. For instance, IFN- γ seems more important for sepsis than TNF- α . For instance, CD28-KO mice [10] reject heart transplants very quickly, due to NK activity. Well-established conclusions can still be overturned in immunology research fairly readily ! Time will tell whether RAGE-KO or any other KO mice will win the prize about to be offered for the longest-living mouse (see <http://www.gen.cam.ac.uk/MM.htm>).

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