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LETTER

HLA-B27-transgenic rats, amyloid deposits, and spondyloarthropathies

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In their very interesting article, Fukunishi and colleagues [1] describe the occurrence of high β_2-microglobulin (β_2m) levels in the serum of rats transgenic for HLA-B27 and β_2m. β_2m-Amyloid deposits in joints, however, were observed exclusively in HLA-B27/β_2m-transgenic animals which had also been treated with collagen type II to induce chronic inflammation. As noted by Fukunishi and co-workers, these results bear some resemblance to the clinical features that can be found in long-term hemodialysis patients [2]. Consequently, the authors suggest that HLA-B27-transgenic rats exhibiting collagen-induced arthritis could be very useful to improve our understanding of hemodialysis-induced arthropathy and amyloid deposits, although they acknowledge also some limitations of this in vivo model system. We would like to point out (1) that another transgenic rat model might be suitable to study the pathogenesis of amyloidosis, and (2) that the importance of these findings extends beyond the field of complications that are often seen as a consequence of hemodialysis.

Amyloidosis has been reported in 6% of ankylosing spondylitis (AS) patients [3], although it seems that those severely affected by AS exhibit a higher incidence (13%) [4]. Therefore, it is likely that the presence of the HLA-B27 gene confers an elevated risk to develop not only AS but also amyloidosis in humans, possibly in connection with other genes [5] or environment-dependent factors such as an inflammation. The HLA-B27/β_2m-transgenic rats [6] thus provide a model for the investigation of two diseases, β_2m-amyloidosis as well as AS, whose pathologies may be difficult to separate. Further in vivo experiments to elucidate the reasons for hemodialysis-induced amyloid deposits might therefore also employ HLA-B7/β_2m-transgenic rats, because these animals do not develop AS-like arthritis [7] and might thus represent a more straightforward model for an investigation of the selective development of β_2m-amyloidosis. If amyloidosis upon treatment with collagen would not develop in HLA-B7/β_2m-transgenic rats, this would constitute a strong argument in favour of a direct involvement of the HLA-B27-transgene in the pathogenesis of both, AS as well as amyloid deposits.

The results obtained by Fukunishi and co-workers [1] are, however, also relevant for AS pathogenesis, although this aspect is not taken into consideration by the authors. They demonstrate that the induction of chronic inflammation is sufficient to trigger β_2m-amyloidosis and amyloid deposits, while Taurog's [6, 7] group has shown that the development of AS-like disease in these transgenic rats depends on the presence of both transgenes, HLA-B27 as well as human β_2m. Furthermore, in a recent study, they were able to establish that a very high copy number of the β_2m-transgene in these animals leads to arthritis and spondylitis of high prevalence, severity, and duration with many parallels to human spondyloarthropathy, apparently as a direct consequence of an increased expression of human β_2m (serum levels of β_2m were not investigated) [8]. All theories that have been proposed over the years to account for the involvement of the *HLA-B27* gene or its product in AS pathogenesis must not only take the results with HLA-B27/β_2m-transgenic animals [1, 6–8] into account, but should also be in line with the presence of pairs of *HLA-B27* alleles ("subtypes") that are differentially associated with AS (for a recent review, see ref. [9]). It seems to us that this double requirement is best fulfilled by the β_2m-deposition hypothesis that considers an

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involvement of the light chain of HLA-B27 molecules as primary cause of AS [10]. This theory assumes that β_2m is released from a subpopulation of cell surface-expressed HLA-B27 molecules of AS-associated subtypes as a consequence of their dissociation due to the loss of suboptimally bound peptides. β_2m could then initiate chronic inflammatory reactions within joints, that finally lead to destructive spondyloarthropathy. Eventually, β_2m might even form amyloid deposits within joints. Therefore, the studies of Fukunishi and colleagues [1] as well as Tran et al. [8] support the central postulate of the β_2m-deposition hypothesis which sees β_2m as the driving force in causing spondyloarthropathies. Furthermore, we would like to point out that AS becomes clinically manifest usually in early adulthood and β_2m-amyloidosis is observed only after many years of hemodialysis, indicating that the development of both diseases is, in addition to other factors, also a time-requiring process.

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