Comment on: The role of environmental heavy metals and the risks for autoimmunity and related rheumatic diseases

Sirs,

We were pleased to read that our research collaboration, beginning in the late 1980s, helped influence Herrera-Esparza *et al*. in writing their review on "The role of environmental heavy metals and the risks for autoimmunity and related rheumatic diseases". As Herrera-Esparza *et al*. note (1), we have contributed a number of novel observations on the mechanisms by which environmental/occupational exposures can lead to autoimmunity (2, 3). Our collaboration had its origins in a fortuitous finding, which we describe below. We also provide some observations on the importance of non-biological exposures in understanding the mechanisms leading to systemic autoimmune disease in humans.

Our story began when one of us (KMP), working in the laboratory of Dr Eng M. Tan at The Scripps Research Institute, isolated the monoclonal autoantibody 72B9 from a lupus-prone NZBWF1 mouse. Subsequently, it was found that 72B9 recognised a highly conserved region of the nucleolar protein fibrillarin, a target of autoantibodies in scleroderma (4). In 1988 PH found that exposure of mice to $HgCl_2$ resulted in anti-nucleolar autoantibodies (ANoA) and renal immune complex deposits in SJL mice (5). Using 72B9 we were able to identify the ANoA response in $HgCl_2$ exposed SJL mice as being against fibrillarin (6). In later studies we showed that the anti-fibrillarin response in murine mercury-induced autoimmunity (mHgIA) is MHC class II restricted and can be elicited by a variety of exposure routes and forms of mercury, and that the expression of disease is heavily influenced by the presence or absence of particular genes (3).

Murine HgIA provided us with a unique model to study the genesis of a specific autoantibody response of importance in systemic autoimmune diseases. However, we soon realised that mercury exposure in mice did not lead to pathology consistent with scleroderma but a relatively mild systemic autoimmunity in non-autoimmune prone mice and acceleration and exacerbation of disease in lupus-prone strains (3). Studies by other research groups also observed that mercury exposure leads to markers of inflammation and autoimmunity but, apart from limited observations, does not lead to autoimmune disease in humans (7, 8). Our experimental studies made clear that mercury exposure results in a spectrum of phenotypes ranging from non-responsiveness to an increasing accumulation of features of asymptomatic autoimmunity, including autoantibodies, inflammatory markers, and tissue pathology (3). In sum, these findings showed that mercury exposure, depending upon genetic background, can elicit features of autoimmunity that may herald but only infrequently leads to clinically diagnosed autoimmune disease.

Evidence that HgIA infrequently progresses to clinically significant autoimmune disease, identifies mHgIA as an important model with which to study the genetic, molecular, and cellular events that limit evolution to clinically relevant disease. We have expanded this concept with a more disease relevant human exposure, silica dust, and the use of outbred mice (2), to show how substantial individual genetic variation impacts the extent of systemic responses to environmental exposures (9). More recently we have shown the importance of subclinical autoimmunity in the development of lupus-like and rheumatoid arthritis-like disease in recombinant inbred mice following silica exposure (10).

The origins of idiopathic autoimmune disease can be difficult to identify, however, environmental and/or occupational exposures can provide relevant triggers with which to uncover early events that precede asymptomatic autoimmunity and that may stimulate or subdue progression to clinical disease. Consideration also needs to be given to the possibility that autoimmunity linked to environmental exposures may exhibit distinct sub-clinical and clinical features.

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