

On a particular IgA1 as substance X in rheumatoid arthritis: a further molecular pursuit of Hench's legacy

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HIGHLIGHT

For more than half a century, various attempts have been undertaken to zero in on the enigma of substance X, a natural molecule that had been postulated by Phil Hench to be responsible for attenuating the course of rheumatoid arthritis during pregnancy and obstructive jaundice. This mystery may have now been solved by the molecular specification presented in this brief report.

ABSTRACT

Recently, the application of the peptide strings concept and its extensions have unravelled a possible dysfunction of a subclass of immunoglobulin A1 molecules as a potentially crucial event for the onset and maintenance of rheumatoid arthritis. Based on additional clinical considerations presented here, it is now proposed that this distinct IgA1 antibody may represent in its functional form the long-sought substance X that had been inferred by Philip Hench in the late 1940s to account for the mitigated course of rheumatoid arthritis during pregnancy and obstructive jaundice. The solution to this major clinical puzzle advanced in this communication may transform the diagnosis and therapy of rheumatoid arthritis in the years to come.

KEY WORDS

Philip Hench, Substance X, Rheumatoid arthritis, Obstructive jaundice, Pregnancy, Immunoglobulin, Antibody, IgG1, Rheumatoid factor, *Candida albicans*, Epitope, Molecular mimicry, Cross-reactivity, Autoimmunity, Diagnosis, Treatment, IgA1, Peptide

Sir,

It has been a long time since Phil Hench communicated his important observations on an improvement of the course of rheumatoid arthritis (RA) during pregnancy and obstructive jaundice (1). Yet, the precise nature of the molecule termed substance X and held responsible for this amelioration has remained elusive to date. Already Hench himself had ascertained that "the responsible agent is neither bilirubin nor a unisexual (female) hormone" (1). Meanwhile, it has also become clear that, although highly effective as therapeutics for RA, corticosteroids are not candidates for substance X either (2).

Recently, my own investigations into the pathogenesis and possible treatment of RA have led me to propose that a certain variant of the immunoglobulin A1 (IgA1) molecule could, most likely as a result of aberrant glycosylation, be dysfunctional in this disease whereas, normally, this distinct subset of natural antibodies would be holding in check the fungus *Candida albicans* and concomitantly concealing a potentially cross-reactive epitope on IgG1 such that it is not a subject for autoimmune reactions (3).

I am now following up on this report (3) by suggesting that such IgA1 isoform may be the long-sought substance X. This conjecture is

supported by the fact that, interestingly, pregnancy and obstructive jaundice share the feature of a significant increase in (local and/or systemic) IgA levels, as measured in saliva in the former condition (4) and in serum in the latter one (5,6). In this context, it is notable that Hench's observation according to which several types of (intrahepatic or extrahepatic, biliary) jaundice had been found to be effective in attenuating RA (1) is entirely consistent with the known increase of IgA as part of these diseases (7). I should specify that among these accumulated IgA molecules there ought to be IgA1 variants that- due, for instance, to saturation of modifying enzymes- have not immediately been inactivated by a post-translational (glycosylation) modification and thus could still assume their putative combined anti-fungal and autoimmunity-preventive role for a given time period.

Therefore, it may be worth examining if (an increase in) the postulated IgA1 fraction could be determined and, if so, these specific immunoglobulins and/or (peptide) mimetics thereof might be employed to reverse RA.

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