Opinion

The immunobiology of aluminium adjuvants: how do they really work?

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Aluminium adjuvants potentiate the immune response, thereby ensuring the potency and efficacy of typically sparingly available antigen. Their concomitant critical importance in mass vaccination programmes may have prompted recent intense interest in understanding how they work and their safety. Progress in these areas is stymied, however, by a lack of accessible knowledge pertaining to the bioinorganic chemistry of aluminium adjuvants, and, consequently, the inappropriate application and interpretation of experimental models of their mode of action. The objective herein is, therefore, to identify the many ways that aluminium chemistry contributes to the wide and versatile armoury of its adjuvants, such that future research might be guided towards a fuller understanding of their role in human vaccinations.

Background

A recent spate of exciting and insightful research papers have, at long last, purported to explain the *modus operandi* of aluminium adjuvants (Al_{ADJ}) [1–7]. Unfortunately, the flurry of review papers that followed the new research have not reached consensus upon the aetiology of the biological activities of Al_{ADJ} [8–10]. Indeed close scrutiny of the new research suggests that an all too liberal application of Occam's razor by scientists and journalists alike was pervasive in them reaching their conclusion that the immunologists' 'dirty little secret' [11] had been revealed. Actually, the recent research, rather than explaining how Al_{ADJ} work, has opened the lid on a Pandora's Box of potential and putative actions of aluminium salts in the context of their use as adjuvants. It has identified many biochemical pathways as potential targets for reactions involving aluminium, and sought to implicate such in immune responses to vaccines that include Al_{ADJ}. The confusion of new information has arisen partly from a recognition of the biological reactivity of aluminium, and partly from the diversity of experimental systems and Al_{ADJ} preparations that were used in past and recent research. There has been a tendency to treat all aluminium salts or preparations as being 'biochemically equivalent' with respect to how physiology reacts to their presence. To date, the majority of attempts to elucidate the mechanism of action of Al_{ADJ} has come from the perspective of immunologists and, possibly, have lacked an understanding of the biological availability of aluminium. Consideration of the bioinorganic chemistry of Al_{ADJ} in light of their immunology should help to consolidate the new information on their modes of action and bring much needed clarity to how they work as clinically approved adjuvants in human vaccinations.

The vaccine and the injection site

The constitution of a vaccine that consists primarily of antigen and Al_{ADJ} is substantially different than that of the physiological milieu into which it is diluted at the injection site. The vaccine preparation is primarily micrometer-sized clusters of nano-sized primary particles of the aluminium salt with which the antigen is associated by adsorption and entrapment [12]. The avidity with which the adjuvant associates with the antigen will depend upon multiple factors, including the form of aluminium salt (usually oxyhydroxide or hydroxyphosphate), the physico-chemical properties of the antigen (including its overall charge and molecular weight), the mode of preparation of the antigen-adjuvant complex (for example, ratio of adjuvant to antigen), and the final solution pH. The latter will usually be around neutral (pH 7.0 ± 0.5), and, along with the highly super-saturated state of the aluminium salt, this will ensure that the concentration of soluble aluminium in the vaccine preparation remains below *ca* 2 μM [12,13]. Similarly, there will be a variable proportion of antigen, often $<1\%$ of the total antigen load, that is not associated directly with the adjuvant [14–16], and some of this 'free' antigen may also be in a complex with aluminium. Injection of this vaccine 'soup' usually involves the dilution of *ca* 0.5 mg of total aluminium into the interstitial fluid at the injection site. The interstitial fluid of the receiving tissue is likely to be pH 7.4, to have an ionic composition similar to plasma, and to be rich in nutrients and metabolites related to tissue growth and function. In short, its composition is very different than that of a vaccine preparation, and in the immediate vicinity of the injection site it will be significantly influenced by its mixing with the vaccine. There will also be ingress of plasma and infiltration of blood cells from the disruption of capillaries as the direct result of the physical consequences of an injection. While there will be an immediate limited migration of some of the smaller or non-particulate forms of the vaccine preparation away from the injection site the

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