A Mechanism of Toxicity of Aluminium-based Adjuvants?

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A general mechanism of vaccine-induced injury?
Who am I? What do we do?
THE BIOGEOCHEMICAL CYCLE OF ALUMINIUM

What is our underlying philosophy?
A Biochemical ‘Tree of Life’ for the Natural Selection of Aluminium

What happens when we do not understand the ‘solution’?
Exley et al.,(2010) The Immunobiology of aluminium adjuvants; how do they really work? Trends in Immunology, 31,103-109
Dilution of the vaccine preparation into the muscle interstitial fluid (MIF) results in an array of potential agonists of the immune cascade, including:

1. $\text{Al}^{3+}$ (aq);
2. free antigen (AG);
3. particulate adjuvant (ADJ);
4. ADJ with associated AG;
5. AG-Al complex;
6. MIF ligand-Al complex;
7. ADJ with associated MIF ligand;
8. MIF ligand-AG complex;
9. particulate iron (as contaminant of adjuvant) either free or with adsorbed Al/AG and resultant reactive oxygen species (ROS);
10. ADJ with associated MIF ligand-AG complex;
11. ADJ with associated MIF ligand-Al complex. MIF ligands might include biomolecules such as; ATP, albumin, transferrin, citrate, fibrinogen.
The array of agonists act upon a number of cell types including;

the resident **muscle tissue** (potentially causing necrotic and/or apoptotic cell death);

infiltrating innate cells such as, **monocytes** (potential for AIADJ-induced differentiation to dendritic cells), **granulocytes** (potential for AIADJ-induced eosinophilia acting directly on B cells), **macrophages** (are known to persist for long periods close to the injection site and may be characterised by inclusions of AIADJ) and **dendritic cells** (DC). The latter may be the major antigen presenting cell (APC)
There are myriad possible modes of interaction between agonists and innate cells including:

(i) toll-like receptor (TLR) binding of AG, AG-Al complex, MIF ligand-AG complex, Al\(^{3+}\)\(\text{(aq)}\)

(ii) multiple TLR binding of AG-ADJ;

(iii) phagocytosis of ADJ, AG-ADJ, MIF ligand-ADJ, MIF ligand-Al complex-ADJ, MIF ligand-AG complex-ADJ;

(iv) direct or indirect binding of Al\(^{3+}\)\(\text{(aq)}\) by membrane receptors and extracellular (lipid membrane) or intracellular (nucleus) activity of ROS.
APCs activate adaptive immunity through;

(a) Nalp3 inflammasome dependent or independent release of chemokines and cytokines (green saucers) including IL-1β and IL-18;

(b) AG presentation by MHC to T cell receptor combined with co-stimulatory molecules;

(c) direct action of ADJ and/or Al$^{3+}$\textsubscript{(aq)} on B/T cells
The Fundaments (Mechanisms) of Al’s Activity as an Adjuvant?
Aluminium salt cytotoxicity leads to the release of danger-associated molecular patterns such as uric acid by the necrotic cell. At high concentrations uric acid forms monosodium urate (MSU) crystals, which are phagocytosed by resident cells. In addition, aluminium salts are directly phagocytosed by the resident cells. MSU crystals or aluminium salts disrupt lysosomes, which results in the release of cathepsin B. Cathepsin B may directly or indirectly induce potassium efflux, which activates the NLR family, pyrin domain containing 3 (NLRP3; also known as NALP3) inflammasome. A signal of unknown origin induces the production of pro-interleukin-1β (pro-IL-1β), pro-IL-18 and pro-IL-33. Caspase 1, which is activated by the NLRP3 inflammasome, cleaves pro-IL-1β, pro-IL-18 and pro-IL-33, thereby inducing the release of the active cytokines and promoting their secretion.
But, does AI simply kill cells?
Adjuvant or Toxicant?
Stimulatory effects of low concentrations of Al both in the vicinity of and away from the injection site, often pro-inflammatory and probably involving pro-oxidant activity of Al.

Box 2. Aluminium facilitates iron-driven biological oxidation

The mechanism that is proposed to underlie this effect involves the formation of the aluminium superoxide semi-reduced radical ion, $\text{AlO}_2^{-2+}$, that acts as a pro-oxidant in both catalyzing the formation of hydrogen peroxide, $\text{H}_2\text{O}_2$, and reducing $\text{Fe}^{3+}$ to $\text{Fe}^{2+}$.

$$\text{Fe}^{2+} + \text{O}_2 \leftrightarrow \text{Fe}^{3+} + \text{O}_2^{-}.$$

$$2\text{O}_2^{-} + 2\text{H}^{+} \rightarrow \text{H}_2\text{O} + \text{O}_2$$

and

$$2\text{O}_2^{-} + 2\text{Al}^{3+} \leftrightarrow 2\text{AlO}_2^{-2+} (2\text{H}^{+}) \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 + 2\text{Al}^{3+}$$

and

$$\text{Fe}^{3+} + \text{AlO}_2^{-2+} \rightarrow \text{Fe}^{2+} + \text{O}_2 + \text{Al}^{3+}$$

thereby facilitates the reaction

$$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{OH}^{-} + \text{HO}^{*} + \text{Fe}^{3+}$$

Redox cycles are integral components of adjuvant-mediated pro-inflammatory signalling [62], and are clear targets for potentiation by aluminium.

Adjuvant or Toxicant?
A role for Al and ATP (ADP etc.)?

Under either scenario, high or low extracellular [ATP], the additional presence of Al would potentiate the effect of ATP.

Al-Adjuvant Sensitisation

Antacids and dietary supplements with an influence on the gastric pH increase the risk for food sensitization

I. Pali-Schöll¹, R. Herzog¹, J. Wallmann³, K. Szalai¹, R. Brunner¹, A. Luksch¹, P. Karagiannis³, S. C. Diesner² and E. Jensen-Jarolim¹

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Sensitisation of BALB mice to ‘codfish’ when fed with an AI antacid!
Specificity of an anti-aluminium monoclonal antibody toward free and protein-bound aluminium

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Could antibodies (immunoglobulins) be raised against Al in vivo?
A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome

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Why is an adjuvant ONLY an adjuvant when and as administered in vaccination?
The Body Burden of Aluminium: What is it?
Yokel et al., (2001). Aluminum bioavailability from drinking water is very low and is not appreciably influenced by stomach contents or water hardness. Toxicology 161, 93-101.
Saiyed and Yokel (2005) Aluminium content of some foods and food products in the USA, with aluminium food additives. *Food Additives and Contaminants* 22, 234-244.
There is (still) too much aluminium in infant formulas

Shelle-Ann M Burrell¹, Christopher Exley²
Vaccine 15, 1314-1318.
Living in ‘The Aluminium Age’ ensures our body burden of Al
When does a body burden of Al become an Al adjuvant?!

When does a body burden of Al become an antigen?!
What is the significance of the location of the Al burden?
Where might aluminium ‘go’ in the brain?

Adapted from Exley (1999) J Inorganic Biochemistry 76, 133-140
What if the Al burden is in the brain?

Exley & House (2011) Monatsh Chem
http://www.springerlink.com/content/9550512205128414/
Therapy?
Facilitated Excretion of Aluminium

Non-invasive therapy to reduce the body burden of aluminium in Alzheimer’s disease

Christopher Exley\textsuperscript{a,*}, Olga Korchazhkina\textsuperscript{b}, Deborah Job\textsuperscript{c}, Stanislav Strekopytov\textsuperscript{a}, Anthony Polwart\textsuperscript{d} and Peter Crome\textsuperscript{c,e}

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The Birchall Centre, Keele University, McMaster University and Ryerson University present the

9th Keele Meeting on Aluminium

Aluminium and Life: Living in the Aluminium Age

Saturday, February 19 to Wednesday, February 23, 2011
Niagara-on-the-Lake, Ontario, Canada

Topics will include all aspects of aluminium from biogeochemistry to health and from physical measurement to biochemical process

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