Could Allergic Contact Dermatitis be a Type 2 Immune Response?

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This is an attempt at a philosophical investigation into the mechanism underlying allergic contact dermatitis.

This investigation is inspired by “Allergic Host Defences” in Nature 2012, by Palm, Rosenstein and Medzhitov [1], in which they expounded a most logical way of looking at first, the functions, and second, one of the dysfunctions, of the immune system.

The article started with dichotomising all the functions of the immune system into: Type 1 immunity vs. Type 2 immunity. (Note: not Th 1 vs. Th 2). This dichotomy makes tremendous sense, and if presented to a student trying to understand Immunology immediately following another dichotomy, that of the organization of the whole of the immune system into innate immunity vs. adaptive immunity, this latter dichotomy also from the pioneering thoughts of Medzhitov (with Janeway) [2], makes the very complex immune system comprehensible. After all, systems are all about organization and functions, and this is the way Immunology ought to be taught.

By Type 1 immunity, the authors meant that arm of the immune system in charge of killing off micro-organisms (viruses, bacteria, protists and fungi), and infected cells (we can infer from this to the killing of transformed cells as well, including malignant cells), using the armamentarium of Th 1 and Th 17 cells, cytotoxic cells and IgM, IgA and several subgroups of IgG.

Inexplicably, they did not mention the important part played by the innate immune system in Type 1 immunity, the part played by germ line encoded pathogen recognition receptors triggering off either a neutrophilic response or a Type 1 interferon response.

By Type 2 immunity, they meant that other arm of the immune system designed to repel or expel 4 categories of risks: helminths, venomous and hematophagous pests, harmful xenobiotics and environmental irritants, using the armamentarium of mast cells, innate lymphoid cells and Th 2 cells, triggering off responses in epithelial tissues, smooth muscles and vasculature, at surfaces that interface with the external environment, which are therefore vulnerable to these 4 risks. The objective is not to kill, but to remove, what may either be too big to kill, or harmful but not alive.

The authors went on to the raison d’etre of their article, which is to opine that what we call allergy is a host response gone wrong, an inappropriate Type 2 immune response.

However, for symmetry as well as for the sake of the hypothetical student trying to understand Immunology, after teaching (a) the organization dichotomized as innate immunity and adaptive immunity and (b) the functions of the immune systems, dichotomized as Type 1 immunity and Type 2 immunity, we should logically discuss dysfunction of Type 1 immunity and Type 2 immunity in order: Type 1 immunity first, before Type 2.

As the authors did not discuss dysfunctions of Type 1 immunity, not being the point of their article, we will make an attempt to extrapolate.

Dysfunctions of type 1 immunity can be dichotomized, again, into two: (a) contributed by the innate immune system and (b) contributed by the adaptive immune system.

Dysfunctional innate Type 1 immunity results in autoinflammatory conditions, and in Dermatology, an example is pustular psoriasis, caused by hypofunctioning IL 36RA.

Dysfunctional adaptive Type 1 immunity is better understood if grouped under another dichotomy. On one arm of this dichotomy, are inappropriate responses against less-than-harmful microbes, infected and transformed cells. We do not recall an established collective term for this, but in Dermatology, an example is plaque type psoriasis, caused by Th 17 cells, against an as yet unidentified, possibly microbial, trigger. On the other arm of the dichotomy, are inappropriate responses against self-antigens. We do have a term for this autoimmunity, and in Dermatology, an example is Pemphigus vulgaris.

Back to the aforementioned article, we follow the thoughts of the authors who opined that allergy is Type 2 immunity gone dysfunctional.

The authors pointed out those allergens are of diverse structures, and listed the following: pollen, shellfish, peanut, bee venom, latex, penicillin and nickel; and set out to explain why all these very disparate things result in the same immune response.

Their contention is that all these disparate allergens, though relatively harmless, all in their different ways; simulate the 4 risks of helminths, venomous and hematophagous pests, harmful xenobiotics and environmental irritants. The immune system is tricked, and triggered, in predisposed persons, to react excessively in order to repel and expel them.
Their argument is so far logical, with one leitmotif, that of an excessive Type 2 immune response, and then, inexplicably, as regards nickel, the authors described allergy to this as a response of Th 1 cells and cytotoxic cells, a dysfunctional Type 1 immunity!

Not only is this reversal against the flow of their thought; importantly, why would the immune system, even if tricked, be tricked into wanting to kill off nickel or nickel “infected” cells?

Backtracking a little, in their article, the authors, in addition to describing two strategies of dealing with the 4 risks, of (a) to expel and (b) to repel, suggested a third strategy, without crafting a term for this. My catch phrase for this third strategy: to dilute.

Considering this, diluting would be the most appropriate way to deal with environmental irritants. In the skin, the epidermis does this job by creating spongiosis, intercellular oedema between keratinocytes held still together by stretched desmosomic junctions, to dilute irritants, and when spongiotic vesicles break, to expel them.

Following the thoughts of the Palm et al again: allergens evoke an excessive Type 2 immune response because they simulate this response, and are interpreted by the immune system as one of the 4 risks.

Contact allergens do indeed simulate irritants. Many contact allergens, like nickel, are electrophilic and will form haptenic attachments to host proteins, and may be interpreted as environmental irritants. Therefore, the immune system of prior exposed persons, especially when the exposure was in a threatening milieu, may mount a completely unnecessary spongiotic immune response when next they see this allergen, in an attempt to dilute this pseudo-irritant. So, following Palm et al’s leitmotif, philosophically speaking, allergic contact dermatitis should be a Type 2 immune response.

Let us imagine what may be happening at a cellular level.

Our thoughts may run something like this imaginary soliloquy:

“If I am a keratinocyte, and I am attacked by an irritant, I will secrete a factor, and I will call this factor a Spongiosis Inducing Factor (SIF), to instruct my neighbours to create some distance from me, yet still hold onto me; and after that secrete fluid to dilute the irritant in the space between us”.

Find a Th 2 cytokine that causes keratinocytes to release fluid into the intercellular space, and you can track it down to the type of lymphocyte that causes allergic contact dermatitis. There is indeed evidence that IL 4 and IL 13 can induce spongiosis (3), supporting the idea of nickel evoking a dysfunctional Type 2 immune response.

REFERENCES

