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Primary prevention of allergic disease

There is now a broad consensus that persistent allergic diseases are most commonly initiated during the first few years of life. The process commences with "recognition" of environmental allergens (usually in foods) by the immature immune system leading to initial weak priming of allergen specific T-cell and then B-cell memory, and this is common to both non-atopic and atopic subjects. In normal individuals, these early responses are eventually terminated via immunoregulatory mechanisms which lead to the development of specific immunological tolerance ("mucosal tolerance") that is driven by T-regulatory (T-reg) cells. However, this control mechanism fails in atopics, and continuing exposure to allergen leads instead to consolidation and expansion of these memory cell populations accompanied by progressively increasing levels of circulating IgE antibodies. This protective regulatory process is "driven" by natural exposure to allergens, and accumulating evidence suggests that one of the most important factors limiting the efficiency tolerance induction is allergen availability. In particular, epidemiological evidence suggests that the shape of the dose response curve describing the relationship between exposure and risk for persistent sensitisation is biphasic, with very low levels of early exposure favouring progressive development of allergen specific Th-memory, while higher levels of exposure selectively drive tolerance induction.

Recent studies from our research group have provided new insight into the mechanism underlying this mucosal tolerance process, and our findings suggest that the rate limiting step is the accumulation by individual dendritic cells (DC) responsible for mucosal immune surveillance of sufficiently high levels of allergen to enable efficient activation of T-reg cells. In particular, in animal strains exhibiting the equivalent of the human "high IgE responder" (atopic) phenotype there appears to be a genetically determined defect in capacity of mucosal DC to efficiently sample allergen from mucosal surfaces: in such strains, the successful induction of protective tolerance to allergen requires much higher exposure levels relative to their "non-atopic" counterparts, and this defect can be overcome experimentally by artificial microenvironmental "allergen loading" of DC by high level exposure.

Translating these findings into the human context, it can be argued that one of the key factors determining the success of tolerogenic immunotherapies targeting the oral mucosa in atopics is the concentration of allergen that can be achieved at the point of contact with DC at mucosal surfaces. This issue will be discussed in the context of sublingual tablet versus soluble allergen exposure of infants, including preliminary findings from our recent trial on oral mucosal immunoprophylaxis in high risk children. In addition, recent studies from our group and others have identified an IgE dependent pathway through which allergen induced inflammation at one mucosal site (e.g. nasal mucosa) can drive the spread of allergic disease to previously unaffected

tissues (e.g. small airways). This pathway involves Th2-driven upregulation of the high affinity IgE receptor on DC precursors in the bone marrow which are responsible for replenishing mucosal DC populations throughout the body. This mechanism provides a new explanation for the phenomenon of the "allergic march" in paediatrics, and supplies a powerful rationale for immunointervention at the early stages of allergy development in at-risk children.

References

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