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Early life development of the immune system

Background

Contrary to traditional concepts, human fetal T-cells are now known to be in a dynamic balance between activation and quiescence, rather than in a passive state of immature inactivity. Fetal T-cells are functionally distinct from those of the adult. They are highly responsive to activation, but also more predisposed to regulatory (Treg) differentiation with higher proportions of circulating Treg in fetal life. This is consistent with growing evidence that T-cell responses (at any age) are in a state of regulated plasticity such that T-cell phenotype can be modulated between 'effector' and 'regulatory' states (rather than a fixed state of terminal differentiation) depending on patterns of gene expression. This fluidity allows adaption to local tissue conditions and is strongly determined by the local tissue milieu.

In pregnancy, locally produced immunomodulatory factors such as TGFbeta and TSLP in placenta and other tissues are important for the regulatory bias in fetal lymphoid tissues. Variations in the local tissue milieu during antigen encounter critically determine the pattern of effector responses and the efficacy of regulatory mechanisms. Accordingly, we have recently shown that variations in the neonatal thymic milieu (TSLP) correlate with the capacity to generate Treg, suggesting differences in the tissue microenvironment in utero. Moreover, we demonstrated that reduced TSLP and reduced Treg in the first weeks of life were associated with the risk of subsequent sensitisation at 1 year.

The importance of these early events is further highlighted by worrying new evidence that a significant proportion of 4-6 month old infants *already* have established egg sensitisation and clinical reactivity (including anaphylaxis) *prior* to the 'first' introduction of egg, stressing the need to define the earlier pathways to sensitisation. Evidence that allergens can cross the placenta, breast milk and the cutaneous barrier provides potential pathways for the initiation of early sensitisation.

The rising rates of allergy in early infancy also indicate that modern environmental changes must be promoting early sensitisation. This means that in the 'modern' context, early allergen exposure may still lead to sensitisation when other environmental conditions are less favourable. A number of environmental factors implicated in the rise of allergic disease are recognised to alter tissue milieu including dietary factors, microbial product and pollutants (smoking). Thus, it is likely that environmental influences in early life exert effects (epigenetic or otherwise) on the milieu in various tissues to promote or protect from allergic disease.

Key message

The dramatic and unprecedented rise in food allergy reinforces the pressing need to define the early events

leading to sensitisation. While regular exposure to ubiquitous proteins such as foods and other innocuous environmental proteins may be a part of developmental processes that promote subsequent clinical tolerance, this may be modified by the environmental factors that modify the local milieu during immune programming.

Summary

Early exposure to ubiquitous allergens is a key part of developmental processes that, if functioning normally, leads to clinical tolerance. Akin to self-tolerance, this may depend on regular, early exposure which if delayed, interrupted or in adverse milieu can break tolerance.

Conclusion

Emergent differences in immune function of newborns destined to develop allergic disease suggest that 'the scene is set' to some extent by birth. It is likely that variations in both the tissue milieu and in allergen encounter (timing, route and dose) influence the initiation and maintenance of tolerance during this dynamic early period.