Prostanoids

Prostaglandin (PG) E2 is a member of the lipid family of prostanoids that are synthesized from arachidonic acid by enzymes, such as COX. PGE2 binds to the 4 receptors EP1 to EP4. It has been described previously that PGE2 stimulates type 1 and type 17 immunity through EP1 and EP4 located at dendritic cells and T cells. Sawada et al now clearly show that PGE2 signaling through EP2 downregulates keratinocyte thymic stromal lymphopoietin production and thus acts as a negative regulator of type 2 immunity.

Identifying this effect of PGE2 now draws a fascinating initial picture on contrasting lipid immune functions (Fig 1). In particular, PGE2 seems to counteract another prostanoid, namely PGD2. PGD2 binds to its receptors, DP1 and DP2, also known as chemoattractant receptor–homologous molecule expressed on T1/2 lymphocytes (CRTH2). Although effects on type 2 immunity in keratinocytes remain to be clarified, PGD2 is known to enhance type 2 immunity through direct action at lymphocytes and indirect effects through dendritic cells (DCs). Furthermore, PGD2 induces eosinophil migration and promotes eosinophil survival.

Thus prostanoids contain lipids that are mutually antagonistic regarding their immune function, with PGD2 being TH2 driving and PGE2 being TH1 and TH17 promoting. These opposing effects are reminiscent of the development of the TH cell concept initiated by Mosmann and Coffman in the mid-1980s. Starting with 2 opposing helper cell subsets, we now have a much more detailed insight into lymphocyte subsets and their specific function in tissue. Even more, these insights led to a new understanding of inflammatory skin diseases and have direct therapeutic consequences because we can now target most lymphocyte subsets with specific therapeutics. Just as the therapeutic intervention of lymphocytes started with panlymphocyte inhibition using drugs, such as methotrexate or cyclosporine, prostanoids are currently being targeted with COX inhibitors that block the synthesis of virtually all prostanoids. In line with this, current therapeutic approaches of supplementing lipids to prevent or treat AE and also other type 2–mediated diseases, such as food allergy or allergic asthma, show inconsistent outcomes. It will be of great interest to neutralize (or enhance) specific lipids, especially prostanoids, to further enhance our understanding of how individual lipids affect the immune system and to pave the way for individualized treatments. Now we have to complete our picture of diseases, such as AE, and lipids to understand the big picture of pathogenesis.
REFERENCES