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DENDRITIC CELLS

# Plasmacytoid dendritic cells in psoriasis

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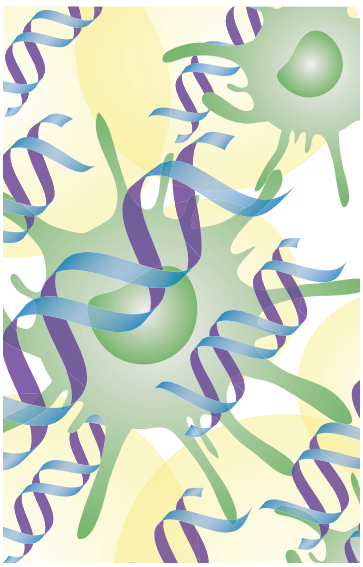
Plasmacytoid dendritic cells (pDCs) are specialized DCs that can produce type I interferons (IFNα and IFNβ) in response to microbial nucleic acids because they express the endosomal Toll-like receptors (TLRs) TLR7 and TLR9. pDCs do not generally respond to self DNA, but in some autoimmune conditions, pDCs are activated and have a role in disease pathogenesis. pDCs are present in psoriatic skin and produce IFNs, but how they become activated in this chronic autoimmune disease is unclear. Now, a study from Michel Gilliet's laboratory shows that the antimicrobial peptide LL37 is responsible for activation of pDCs in psoriasis.



Knowing that pDCs are activated in psoriasis, the authors first wanted to identify the trigger factor. To do this, they stimulated peripheral-blood pDCs with extracts from psoriatic or normal human skin that had been separated by reversed-phase high-performance liquid chromatography (HPLC) into different fractions. Extracts from normal skin were unable to stimulate IFN production from pDCs, but one fraction from psoriatic skin was able to do so. Two major components were identified in this fraction, corresponding to the peptides psoriasin and LL37 (the only known human cathelicidin — a type of antimicrobial peptide). Using synthetic peptides it was shown that only LL37 could stimulate pDCs and its activity could be completely blocked using an LL37-specific antibody.

So, how does LL37 stimulate pDCs? An obvious starting point, given that pDCs are specialized sensors of nucleic acids, was to look for a role for DNA. Dying cells in LL37-stimulated pDC cultures release self DNA, and depletion of the self DNA by DNase treatment blocked the induction of IFNα expression. Mixing human DNA with LL37 prior to adding it to pDC cultures resulted in a dose-dependent increase in IFNα production.

Next the authors investigated whether LL37 converts self DNA into a pDC trigger by forming a complex with the DNA. Size-exclusion HPLC confirmed that LL37 binds to DNA and induces the formation of condensed, aggregate forms of DNA. So, do endosomal TLRs have a role in the recognition of such complexes? Chloroquine, which is an inhibitor of endosomal acidification and prevents endosomal TLR signalling, inhibited IFNα production by LL37–DNA-stimulated pDCs, suggesting that an endosomal TLR was involved. Treatment of pDCs with a short oligonucleotide that specifically blocks TLR9 inhibited the production of IFNα induced by LL37–DNA complexes. Confocal-microscopy experiments showed that LL37–DNA complexes are internalized into and retained in early endosomal compartments, consistent with recent studies showing that TLR9 signalling in early endosomes leads to IFNα production.

This study shows that psoriasis is probably induced as a result of skin damage that leads to the release of LL37, which, together with self DNA, triggers pDCs to produce type I IFNs that in turn lead to the activation of autoimmune T cells and the pathogenesis of psoriasis.

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**ORIGINAL RESEARCH PAPER** Lande, R. *et al.* Plasmacytoi d dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* 16 September 2007 (doi:10.1038/nature06116)