

## Defensins And Defensin-Like Chemokines at the Ocular Surface with

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### Which defensins are expressed at the ocular surface?

**Alison M. McDermott:** The ocular surface comprises the squamous epithelia of the cornea and conjunctiva. As with all epithelial tissues, they form a protective barrier that defends against invading pathogens. One of their roles is the production of antimicrobial peptides such as  $\beta$ -defensins. These peptides are characterized by the presence of six conserved cysteine residues that form three disulphide bonds, and have potent antimicrobial activity against a variety of bacteria, fungi and viruses.

Ocular surface defensin expression has been studied by a number of investigators (1). We have observed that under normal circumstances both corneal and conjunctival epithelial cells express human  $\beta$ -defensin (hBD)-1 and hBD-3 (2,3). Then in the presence of infection, inflammation and during wound healing hBD-2 is also expressed (1-4). A recent study indicates that hBD-4 mRNA is also expressed at the ocular surface,

although the significance of this will only be apparent if presence of the actual peptide is confirmed (5). Thus, hBD-1 and hBD-3 contribute to baseline defence against pathogens, with hBD-2 being additionally expressed under certain conditions. As the defensins all have differing spectra of antimicrobial activity, additional expression of hBD-2 will afford extra protection. Furthermore, as defensins are known to modulate various mammalian cell behaviours, we hypothesize that hBD-2 in particular, because it is specifically upregulated after injury, may have non-microbicidal roles such as modulating ocular surface wound healing (see figure).

In addition to defensins, the ocular surface epithelia also express the cathelicidin LL-37 (6), CAP37 (7) and probably several other antimicrobial peptides (5) which also contribute to antimicrobial protection and which may have effects on epithelial cell behaviour.

constitutively expressed by all epithelial tissue and its expression is not modulated by cytokines. The expression of hBD-3 is increased by TNF $\alpha$  in keratinocytes and airway epithelial cells (8), although we have not found this to be the case for ocular surface epithelial cells.

The effect of various cytokines on expression of hBD-2 has been extensively studied. Pro-inflammatory cytokines such as IL-1 and TNF $\alpha$  are known to be potent inducers/upregulators of hBD-2 expression in many epithelial tissues, including the ocular surface (2,3). We have investigated the

pathways leading to IL-1 mediated hBD-2 expression in corneal epithelial cells and observed that activation of NF $\kappa$ B, tyrosine kinases, p38 MAP kinase and JNK are essential for upregulated expression of the peptide (2). Similar findings have been reported for a variety of epithelial tissues (9).

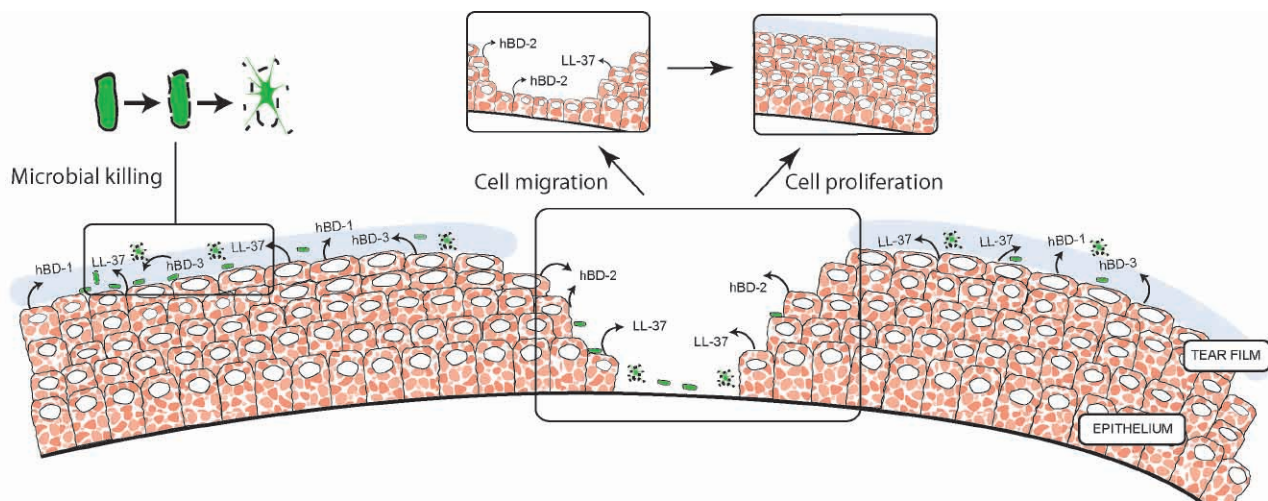
As hBD-2 is not typically expressed by ocular surface epithelia, it is likely that pro-inflammatory cytokines such as IL-1 released in response to injury and infection cause upregulation of the peptide thus enhancing antimicrobial protection.

### How important are $\beta$ -defensins for protection against infection?

**Alison M. McDermott:** This is a very difficult question to answer as the production of  $\beta$ -defensins is but one of an extensive array of weaponry which the body uses to defend itself against infection. Loss of the ability to produce  $\beta$ -defensins may not have a significant effect if all (or most of) the remaining innate defence mechanisms are intact. However if several innate defence mechanisms are breached, then epithelial production of  $\beta$ -defensins may become the primary defence against a particular infection. Thus, the relative importance

of  $\beta$ -defensins lies in the robustness of other innate defence mechanisms and, as defensins have varying spectra of antimicrobial activity, is likely to be pathogen dependent.

Defensin deficiency has recently been linked to Crohn's disease, a chronic inflammatory disease of the intestinal mucosa (10). Here loss of the protective defensin barrier in the intestine is suggested to lead to increased bacterial invasion, which induces an inflammatory response. Knocking out the mouse  $\beta$ -defensin-1 gene led to delayed clearance of *Haemophilus influenzae* from



### Are cytokines involved in the expression of $\beta$ -defensins?

**Alison M. McDermott:** Yes, cytokines have been shown to modulate

the expression of some defensins. hBD-1 is generally accepted to be

the lung (11) and an increase in *Staphylococcus* colonisation in the bladder (12). Together, these studies provide evidence

that defensins do indeed have activity *in vivo* and so are an important component of innate immunity.

## What are defensin-like chemokines?

**Alison M. McDermott:** Chemokines are cytokines that act as chemoattractants and as such have important roles in regulating leukocyte participation in inflammation and immunity. They are divided in to four groups based on the number and arrangement of conserved N-terminal cysteine motifs: C, CC, CXC and CX<sub>3</sub>C, where X is a non-conserved amino acid (13). Some defensins have a conserved CXC region at the N-terminus

and are chemotactic for leukocytes (9). Because of these, and other similarities between defensins and certain chemokines, Cole et al. (14) explored the antimicrobial activity of some chemokines. They observed that CXCL9, CXCL10 and CXCL11 (all members of the interferon- $\gamma$ -inducible (ELR) group of CXC chemokines) had substantial antimicrobial activity. Thus these chemokines are sometimes referred to as "defensin-

like chemokines".

In a recent study by Harvey et al. (15) CXCL10 (IP-10) and CXCL11 (I-TAC) were upregulated in conjunctival epithelial cells in response to adenoviral infection. Furthermore, these defensin-like chemokines were directly active against respiratory adenovirus serotypes Ad3 and Ad5. Thus, CXCL10 and CXCL11 can be added to the ever-increasing list of peptides with antimicrobial activity expressed by the ocular surface epithelia.

## REFERENCES

1. McDermott AM Ocular Surface 2, 229, 2004
2. McDermott AM et al. Invest Ophthalmol Vis Sci 44, 1859, 2003
3. Narayanan S et al. Invest Ophthalmol Vis Sci 44, 3795, 2003
4. McDermott AM et al. Curr Eye Res 22, 64, 2001
5. McIntosh RS et al. Invest Ophthalmol Vis Sci 46, 1379, 2005
6. Gordon YJ et al. Curr Eye Res 30, 385, 2005
7. Ruan X et al. Invest Ophthalmol Vis Sci 43, 1414, 2002
8. Harder J et al. J Biol Chem 276, 5707, 2001
9. Yang D et al. Ann Rev Immunol 22, 181, 2004
10. Wehkamp J et al. J Leukoc Biol 77, 460, 2005
11. Moser C et al. Infect Immun 70, 3068, 2002
12. Morrison G et al. Infect Immun 70, 3053, 2002
13. Laing KJ et al. Dev Comp Immunol 28, 443, 2004
14. Cole AM et al. J Immunology 167, 623, 2001
15. Harvey et al. Invest Ophthalmol Vis Sci 46, 3657, 2005