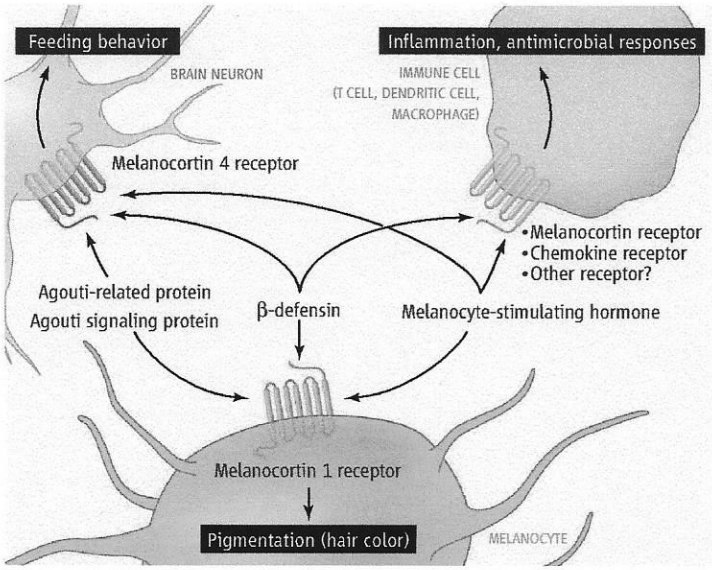
GENETICS

# β-Defensin Repertoire Expands

How does a peptide involved in fighting microbial infections also control hair color in mammals?

**Julia R. Dorin and Ian J. Jackson**

β-Defensins are antimicrobial peptides of key interest because they operate in both innate and adaptive immune responses in mammals (*1*). Now, these peptides have become more intriguing. On page 1418 of this issue, Candille *et al.* (*2*) identify a role for a β-defensin in pigmentation. The peptide, CBD103, binds to melanocortin 1 receptor, one of a protein family that controls pigmentation, inflammation, and feeding behavior. This expands the functional repertoire of β-defensins and opens new avenues of research with potential implications for human disease (see the figure).




**Beyond defense.** β-Defensins bind to melanocortin receptors, extending the influence they may have on biological processes.

How does a gene implicated in mammalian immune responses alter pigmentation? A mutation at the $K^B$ locus was identified as the cause of dominant inheritance of a black coat in dogs (*3*). Candille *et al.* identify the gene at this locus as *CBD103*, the dog ortholog of human *DEFB103*, which encodes the β-defensin HBD3. The $K^B$ mutation results in loss of the predicted first amino acid of mature CBD103. Mutant CBD103 is more efficiently secreted from cells and has a higher affinity than the wild-type peptide for the dog melanocortin 1 receptor, which controls production of eumelanin, the black/brown hair pigment.

CBD103 also competes with agouti signaling protein for binding to this receptor. Agouti signaling protein antagonizes the melanocortin 1 receptor, resulting in the production of pheomelanin, a red/yellow pigment. Wild-type and mutant CBD103 suppressed agouti signaling protein in transgenic mice, resulting in black hair rather than agouti (hair with a yellow stripe). A reasonable conclusion is that increased abundance and stronger affinity for the melanocortin 1 receptor allows mutant β-defensin to competitively inhibit agouti signaling protein in melanocytes, enabling the production of eumelanin and black hair.

There is a conundrum, as the β-defensin also competes with α-melanocyte–stimulating hormone (a melanocortin) to bind melanocortin 1 receptor, yet it does not itself elicit adenosine 3′, 5′-monophosphate signaling that characterizes this receptor's activation. So how does this receptor elicit black pigment production in response to CBD103? Perhaps the dog receptor has ligand-independent signaling, as seen in the mouse (but not human), in which lack of α-melanocyte-stimulating hormone has little effect on pigmentation (*4*). Alternatively, CBD103 may activate different effectors through the melanocortin 1 receptor.

Two human β-defensins, HBD1 and HBD3, bind to the melanocortin 1 receptor, but there is little sequence similarity between them (though tertiary structure is conserved) (*1*). There are some structural similarities between agouti signaling protein and β-defensins—both are cationic, with antiparallel β sheets stabilized by cysteine bridges. These properties may be important for receptor interaction.

Although HBD3 is highly expressed and present in inflamed psoriatic skin (*5*), patients do not show hyperpigmentation to in-dicate melanocortin 1 receptor activation. HBD3 attracts certain immune cells (including monocytes, macrophages, and mast cells) through an as yet unidentified receptor, and immature dendritic cells and memory T cells through chemokine receptor 6 (*1*). HBD3 expression increases in response to proinflammatory agents, and it also induces production of proinflammatory cytokines (*1*). Some melanocortins suppress inflammation (*6*). β-defensins may act at melanocortin receptors to modulate inflammation.

Candille *et al.* also observed that transgenic mice overexpressing the dog β-defensin have lower body weight. It's possible that CBD103 activates the melanocortin 4 receptor, suppressing feeding behavior. Alternatively, reduced body size might reflect peptide toxicity due to overexpression. Determining immune dysfunction in these transgenic mice should tease out the answer.

Does the mutated β-defensin alter host defense? Transgenic mice that overexpress human α-defensin show increased resistance to pathogens (*7*). But the amino-terminal residues of β-defensin are important for antimicrobial action against *Staphylococcus aureus*, a common skin pathogen, so mutant CBD103 could have lost function. In mice, loss of β-defensin 1 reduces clearing of *S. aureus* and *Haemophilus influenzae* (*8*, *9*). The immune phenotype of dogs carrying the mutation warrants investigation. Variation in copy-number and expression of human defensins is seen in normal populations and in patients with Crohn's disease, an inflammatory disorder of the intestinal tract (*10*). Interaction of β-defensins with pleiotropic melanocortin receptors may cause subtle phenotypic changes with direct relevance to human disease.

The authors are in the MRC Human Genetics Unit, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. E-mail: ian.jackson@hgu.mrc.ac.uk

**References**

1. M. Pazgier *et al.*, *Cell. Mol. Life Sci.* **63**, 1294 (2006).
2. S. I. Candille *et al.*, *Science* **318**, 1418 (2007); published online 18 October 2007 (10.1126/science. 1147880).
3. J. A. Kerns *et al.*, *Mamm. Genome* **15**, 798 (2004).
4. I. J. Jackson *et al.*, *Hum. Mol. Genet.* **16**, 2341 (2007).
5. I. Nomura *et al.*, *J. Immunol.* **171**, 3262 (2003).
6. C. Maaser, K. Kannengiesser, T. Kucharzik, *Ann. N.Y. Acad. Sci.* **1072**, 123 (2006).
7. N. H. Salzman *et al.*, *Nature* **422**, 522 (2003).
8. G. Morrison *et al.*, *Infect. Immun.* **70**, 3053 (2002).
9. C. Moser *et al.*, *Infect. Immun.* **70**, 3068 (2002).
10. K. Fellermann *et al.*, *Am. J. Hum. Genet.* **79**, 439 (2006).

10.1126/science.1151370





Published by AAAS