



Published in final edited form as:

*Semin Cutan Med Surg.* 2008 June ; 27(2): 144–150. doi:10.1016/j.sder.2008.04.002.

## Antimicrobial Peptides, Skin Infections and Atopic Dermatitis

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### Abstract

The innate immune system evolved over 2 billion years ago to first recognize pathogens then eradicate them. Several distinct defects in this ancient but rapidly responsive element of human immune defense account for the increased incidence of skin infections in atopics. These defects include abnormalities in the physical barrier of the epidermis, alterations in microbial pattern recognition receptors such as toll receptors and NOD, and a diminished capacity to increase the expression of antimicrobial peptides during inflammation. Several antimicrobial peptides are affected including; cathelicidin, HBD-2, and HBD-3, which are lower in lesional skin of atopics compared to other inflammatory skin diseases, and dermcidin, which is decreased in sweat. Other defects in the immune defense barrier of atopics include a relative deficiency in plasmacytoid dendritic cells. In the future, understanding the cause of these defects may allow therapeutic intervention to reduce the incidence of infection in atopic individuals and potentially decrease the severity of this disorder.

### INTRODUCTION

Patients with atopic dermatitis (AD) have an increase in clinically apparent staphylococcal infections and some cutaneous viral infections. Several important recent findings in patients with this disorder have provided an explanation for this increased susceptibility through improved understanding of the innate immune barrier that the skin provides against microbial pathogens. Defects in the epidermal barrier, in conjunction with defects in the pattern recognition receptors and reduced production of antimicrobial peptides in the innate immune system of atopics, all contribute to the increase susceptibility to cutaneous infections in patients with AD.

#### A Bad Start for Atopics, failure of the Barrier...

The first element of the innate immune defense system is the physical barrier presented by the epidermis. Not surprisingly, a significant proportion of patients with AD have an abnormality in this barrier. This may be partially explained by observations of altered or absent production of the structural protein filaggrin. Filaggrin is essential for epidermal barrier formation and hydration<sup>1</sup>. To date, 17 loss of function nonsense or frameshift mutations in filaggrin have been identified.<sup>2–4</sup> These filaggrin mutations have been shown to be a major predisposing factor to the development of AD<sup>5</sup>, asthma and allergic rhinitis<sup>6,7</sup> Furthermore, null mutations in the filaggrin gene seem to be indicative of a more severe, persistent phenotype, as they are

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associated with an early onset AD phenotype that persists into adulthood<sup>8,9</sup>, as well as increased asthma severity<sup>10</sup>

These mutations in filaggrin on a molecular level, support the clinical observation of improvement in AD with daily emollient use, use of mild soaps, and reduction in exposure to water. An intact epidermal barrier is an important first line component of the ability of atopics to fight infections.

### **Recognizing Microbes, the next big burden for AD...**

Although the defects in filaggrin in the epidermal barrier play an important role in the development of cutaneous infections in AD, the immune barrier of AD patients is compromised at several levels. The combination of epidermal barrier defects and an impaired microbial recognition and response system all contribute to the increased incidence of skin infections in atopics.

### **The Innate Immune system**

When the atopic barrier is compromised, the second layer of protection by the host is through the system of microbial recognition and response inherent to all living organisms. This mechanism of innate immunity evolved over 2 billion years ago, and is the primary defense for plants and animals, vertebrates and invertebrates.<sup>11-13</sup> In most organisms, this essential component of innate immunity is a collection of nonspecific, pre-existing anatomical and cellular mechanisms to combat infection. The innate immune system responds to a pathogen in two ways: (1) it recognizes invading pathogens and distinguishes pathogenic from nonpathogenic microorganisms (2) it starts a coordinated physiological response to kill pathogens.

The innate immune system recognizes invading pathogens through pathogen associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs). PRRs are present both intracellularly, on cell membranes, and in circulating plasma and tissues.<sup>14-16</sup> Best known of the PRRs are the toll receptors, which are structurally related to the drosophila toll receptor and the interleukin 1 receptor, and are expressed in human keratinocytes and antigen-presenting cells.<sup>17,18</sup> TLRs are transmembrane proteins with a leucine rich extracellular domain, and a highly conserved intracellular domain.<sup>19</sup> To date, ten TLRs have been identified, with each receptor characterized by the microbial ligand it recognizes.<sup>20</sup> The extracellular portion is responsible for specific ligand recognition, and the intracellular portion mediates signal transduction through coupling with different adaptor molecules. At least four different adaptor molecules are known: MyD88, TIR-domain containing adaptor, TIR domain containing adaptor protein inducing IFN- $\beta$  (TRIF), and the TRIF related adaptor molecule. Most TLRs utilize the adaptor molecule MyD88 which in turn activates the MAPK kinases and the transcription factor NF- $\kappa$ B leading to the expression of several proinflammatory and regulatory cytokines and chemokines, including IL- $1\beta$ , TNF- $\alpha$ , IL-6 and IL-12.<sup>21</sup>

Examples of PAMPs include lipopolysaccharides (lps) from gram negative bacteria, lipoteichoic acid and peptidoglycan from gram positive bacteria, and mannans of yeast/fungi. Each TLR has been found to recognize specific PRRs. TLR2 is a heterodimer that associates with TLR1 or TLR6 and CD14 to recognize lipopeptides from bacteria peptidoglycan and lipoteichoic acid(LTA). TLR3 recognizes double stranded RNA produced during viral replication, and TLR4/CD14 recognizes lps from gram negative bacteria. Flagellin is recognized by TLR5, and viral single stranded RNA by TLR7 and TLR8. TLR9 recognizes unmethylated CpGDNA found primarily in bacteria. TLR 11 recognizes uropathogenic E coli.<sup>22</sup> Polymorphisms of TLR2 (Arg753Gln) located within the intracellular part of the receptor, has been associated with staphylococcus aureus infection, and is present in higher frequency in

AD patients compared to controls.<sup>23</sup> These patients also have an increased disease severity with high IgE antibodies to staphylococcus aureus superantigens.

Intracellular PAMPs such as peptidoglycan are recognized by nucleotide binding oligomerization domain (NOD) NOD 1 and NOD 2.<sup>24</sup> NOD1 senses diaminopimelic acid-type PGN produced by gram negative bacteria, and NOD 2 senses muramyl dipeptide found in PGNs from all bacteria including staphylococcus aureus.<sup>24</sup> Polymorphisms in the NOD 1/caspase recruitment domain containing protein (CARD) 4 have been associated with AD. Interestingly, these polymorphisms were also associated with asthma and total serum IgE levels, but not with allergic rhinoconjunctivitis.<sup>25</sup>

CD14 is a multifunctional receptor for LPS and other bacterial wall components.<sup>25</sup> CD14 binds LPS and LPS binding protein and is required for LPS induced macrophage activation via TLR4. It has also been found to induce cellular activation in response to LTA through a TLR2 dependent pathway<sup>26</sup> and has binding activity for peptidoglycans.<sup>27</sup> Reduced levels of CD14 has been observed in atopic children.<sup>28</sup> In breast fed children, low levels of soluble CD14 in breast milk had been associated with an increased risk for AD and asthma.<sup>29,30</sup>

These defects in the pattern recognition receptors, which are the first line of defense in the innate immune system reduce the ability of AD patients to recognize cutaneous microbial pathogens resulting in an increase in their incidence of bacterial and viral infections.

### Responding to microbes, the role of Antimicrobial peptides

In the 1980s, Hans Boman identified a 37 amino acid cationic peptide from hemolymph of the cecropia moth after injection of bacteria.<sup>31</sup> The peptide was devoid of disulfide bonds, had a linear alpha-helical structure, and exhibited antimicrobial activity against gram negative bacteria. This family was classified under the cecropin family of AMPs. Since this time, other AMPs have been identified with variable activity against bacteria, fungi and viruses. We now understand that the AMPs represent an essential system that the skin uses to respond and prevent the uncontrolled growth of microbes. Unfortunately for the patient with AD, AMPs in human skin such as defensins, cathelicidins, and dermcidin have all been shown to have diminished expression and function compared to that expected when normal skin is injured. Better understanding of these molecules sheds further light on the mechanisms responsible for infections in AD.

### Defensins

Originally identified in human and rabbit neutrophils,<sup>32</sup> defensins are cationic peptides containing cysteine rich conserved motifs. There are three subfamilies of defensins, which include alpha, beta, and circular theta defensins. Alpha and beta defensins are distinguished by the position of three disulfide bridges. Alpha defensins have been identified in neutrophils and in the Paneth cells of the small intestine.<sup>33</sup> Human beta defensins 1–4 are expressed in keratinocytes. The theta defensin pseudogene has been found in human bone marrow, but the peptide has not been identified in humans.<sup>34</sup> Of the four human beta defensins, only HBD-1 is constitutively expressed in the human epidermis and sweat gland ducts.<sup>35–37</sup> HBD 2–3 are inducible by bacterial infection, cytokines IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , and differentiation.<sup>38,39</sup> HBD2–4 can be induced by calcium and phorbol 12 myristate 13 acetate (PMA) and can be inhibited by retinoic acid pretreatment.<sup>40</sup> HBD-2 is highly sensitive to the physiologic environment, and shows preferential antimicrobial activity toward gram negative bacteria such as Escherichia coli and Pseudomonas.<sup>41</sup> Because of HBD-2's high sensitivity, high salt concentrations such as that found in sweat can substantially reduce the antimicrobial capacity of HBD-2.

Alpha and beta defensins show a broad antibacterial activity against gram positive and negative bacteria,<sup>32,42</sup> fungi,<sup>43,44</sup> and viruses, including adenovirus,<sup>45</sup> papilloma virus,<sup>46</sup> human immunodeficiency virus (HIV),<sup>47,48</sup> and the human herpes simplex virus (HSV)<sup>49</sup>. Binding of the positively charged defensin with the negatively charged bacterial membrane precedes membrane permeabilization and is thought to be the mechanism of bacterial killing by the defensins.

Defensins also induce cytokines. Alpha defensins upregulate the expression of TNF- $\alpha$  and IL-1 $\beta$  in monocytes activated with staphylococcus aureus.<sup>50</sup> Defensins induce IL-8 and proinflammatory cytokines in lung epithelial cells,<sup>51,52</sup> and IL-18 in primary keratinocytes.<sup>53</sup>

## Cathelicidins

Cathelicidins were originally named for a diverse group of peptides based upon their evolutionally conserved cathelin-like-N-terminal domain and their structurally variable cationic antimicrobial C terminal domain.<sup>54</sup> The cathelin like domain is similar to the 12 kD protein, cathelin, which was originally isolated as a cathepsin L inhibitor.<sup>55</sup> Most cathelicidins are amphipathic cationic peptides which are alpha helical in some buffer conditions.<sup>56</sup> The amphipathic structure and cationic charge allows the cathelicidin peptides to interact in the aqueous environment, the lipid rich membrane, and bind to the negatively charged bacterial membranes.

There are two major steps to cathelicidin expression and function. Transcription to mRNA, and post-translational processing to active peptides. In the human genome, cathelicidin exons 1–4 are on chromosome 3p21. They are transcribed as a single gene called cathelicidin antimicrobial peptide (CAMP) which translated to the proprotein termed human cationic antimicrobial protein 18kDa or hCAP 18 which is inactive as an antimicrobial peptide.

In the skin, hCAP 18 is stored in the lamellar bodies in keratinocytes and secreted in the granular and spinous layer of the epidermis.<sup>57</sup> After secretion stratum corneum tryptic enzyme, kallikrein 5/hK5) first process hCAP 18 to LL-37, and a combination of SCTE and SCCS (stratum corneum chymotryptic protease, kallikrein 7/hK7) further process the smaller peptides to RK-31 and KS-30.<sup>58,59</sup> In human keratinocytes cathelicidin is inducible with wounding, infection, and skin inflammation from basal expression levels that are low and barely detectible.<sup>60</sup> 1,25 Dihydroxyvitamin D is also a potent inducer of cathelicidin mRNA transcription, and the presence of Vitamin D3 is essential to cathelicidin induction in skin infection and wounding.<sup>61–63</sup> Interestingly, in mice, who are typically nocturnal, the cathelicidin gene for MCRAMP (Cnlp) derived from phagocytes, is regulated by hypoxia inducible factor 1 alpha (HIF-alpha).<sup>64,65</sup> LL-37 consists of 37 amino acids starting with two leucines, and is expressed in various cells, tissues and body fluids, including epidermal keratinocytes and intestinal cells,<sup>62</sup> T cells,<sup>66</sup> mast cells,<sup>67</sup> neutrophils,<sup>68</sup> wound fluids,<sup>69</sup> bronchoalveolar lavage fluids,<sup>70</sup> sweat,<sup>71</sup> saliva,<sup>72</sup> and vernix caseosa of newborns.<sup>73</sup> Cathelicidins are cationic, and thought to directly bind to the anionic cell wall and membrane of the microbe, increasing permeability of the microbes cell wall.<sup>74,75</sup> Through this method of killing they have a broad antimicrobial activity against gram positive and negative bacteria,<sup>76–78</sup> vaccinia virus,<sup>79</sup> and fungi.<sup>80,81</sup>

Cathelicidins also induce proinflammatory cytokine secretion. They stimulate IL-8 secretion from human epidermal keratinocytes via direct or indirect activation of the epidermal growth factor receptor.<sup>82,83</sup> Both beta defensins and LL-37 induce production of IL-6, IL-10, and the chemokines (interferon inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 3 alpha, RANTES), in keratinocytes, allowing them to work in both innate and adaptive immunity.<sup>84</sup> LL-37 is chemoattractive to neutrophils, monocytes and T cells by activating the G protein coupled receptor FPRLs (formyl peptide receptor like 1).<sup>85</sup>

## Dermcidin

The dermcidin gene and mature peptide have been identified only in humans to date. They are constitutively secreted in human sweat and not inducible by skin injury or inflammation.<sup>86</sup> Dermcidin is secreted as a proprotein, and post secretory processing by cathepsin D cleaves the peptide from the C terminus of the proprotein thus allowing for the dermcidin peptides to be distributed to the skin surface in sweat.<sup>87</sup> Dermcidin is an anionic peptide whose specific method of killing of microbes is still unknown, however they have been shown to have potent antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and candida.<sup>88</sup>

## Staphylococcal infections and the cytokine milieu of AD

Healthy skin of normal individuals has shown colonization of a large number of microorganisms which include *Staphylococcus epidermidis*, *Staphylococcus hemolyticus*, and *Staphylococcus hominus*.<sup>89</sup> Colonization by *Staphylococcus aureus* occurs in approximately 5% of the healthy population.<sup>90</sup> In contrast, more than 90% of atopics have *Staphylococcus aureus* colonization on their lesional and to a lesser extent, their nonlesional skin.<sup>91</sup> The impaired skin barrier function may partially explain *Staphylococcus aureus* colonization in AD, however psoriatics, who also have a disrupted skin barrier are in comparison much more resistant to skin infections.<sup>92</sup> Differences in resistance to cutaneous infections may be partially explained by the disrupted barrier, and differences in the cytokine milieu resulting in differential antimicrobial expression between psoriatics and atopics.

Ong et al, was first to identify a deficiency in LL-37 and HBD-2 in atopic lesional skin compared to those of psoriatic lesional skin.<sup>93</sup> Because AMPs can be induced in wounding and inflammation, it was initially expected that both the psoriatic and atopic lesional skin would have an elevation in AMPs. Quantitative real-time reverse transcriptase polymerase chain reaction assays examining the relative expression of HBD-2 and LL-37 mRNA found significantly decreased levels of both AMPs in acute and chronic lesions of atopic dermatitis. Subsequently, Nomura et al, found reduced expression of HBD-3 by real time PCR and immunohistochemistry.<sup>94</sup> Because LL-37, HBD-2 and HBD-3 all have anti-staphylococcal activity, this observed decrease in AMPs is thought to be an important factor in staphylococcal colonization and infections of atopic subjects.

The cytokine milieu in atopics is now thought to play a significant role in the reduction of AMPs. AD exhibits a Th2 directed cytokine pattern with high IgE levels and eosinophilia. The Th2 cytokine pattern is characterized by overexpression of IL-4, IL-10 and IL-13.<sup>95-97</sup> High levels of IL-4 and IL-13 inhibit HBD-2 and HBD-3.<sup>98,99</sup> IL-4 and IL-13 act directly on keratinocytes to downregulate the expression of HBD-3 and LL-37 through activation of STAT-6 which inhibits the TNF- $\alpha$ /NF $\kappa$ B system.<sup>100,101</sup> Thus the reduction in AMP expression in atopic lesional skin is thought to be secondary to the inhibitory effects of IL-4 and IL-13 on TNF- $\alpha$  and IFN- $\gamma$  stimulation in keratinocytes and the indirect effect of the immunomodulatory cytokine IL-10 on proinflammatory cytokine production by infiltrating cells.<sup>95,101</sup>

High levels of IL-4 and IL-13 also inhibit IL-8 and iNOS gene expression.<sup>102,103</sup> IL-8 is a chemokine that attracts PMNs into the skin where they phagocytose and kill bacteria, and iNOS can kill viruses, bacteria and fungi through production of nitric oxide; thus both are important mediators of innate immunity.

IFN- $\gamma$  is considered a key cytokine of innate and adaptive immunity. Its role in host defense against microbial pathogens is through activation of monocytes, macrophages, NK cells, enhancing antigen processing and presentation and modulation of the humoral response. Thus a deficiency may result in an hampered pathogen elimination and increased propensity to skin

infections in AD.<sup>104</sup> Clinically, increased *Staphylococcus aureus* skin colonization in AD directly correlates with an increase in the atopic dermatitis clinical severity as measured by the Scoring Atopic Dermatitis index (SCORAD) index, and is inversely correlated with a decreased IFN- $\gamma$  production by peripheral blood CD4 and CD8+ T cells.<sup>105</sup>

The antimicrobial peptide dermcidin has also been shown to be decreased in atopics.<sup>106</sup> It is constitutively expressed in eccrine sweat glands and secreted into sweat. Several dermcidin derived peptides are significantly reduced in AD compared to healthy subjects, and atopics with previous bacterial or viral infections show the lowest concentration.<sup>106</sup>

Adherence of *Staphylococcus aureus* to the skin surface are also increased in AD compared to healthy subjects.<sup>107,108</sup> The adhesions of *Staphylococcus aureus* takes place primarily in the stratum corneum, and is mediated by fibronectin and fibrinogen. The fibronectin binding protein of staphylococcus is a bifunctional protein that binds to fibrinogen.<sup>109</sup> IL-4 appears to play a role in the staphylococcal binding to the skin. IL-4 induces the synthesis of fibronectin by skin fibroblasts.<sup>103</sup> Fibronectin in combination with plasma exudation of fibrinogen allows staphylococcus to bind to the skin.<sup>107,108</sup> In the murine model, binding of staphylococcus did not occur in IL-4 gene knockout mice.<sup>103</sup> These staphylococcal mutants that were deficient in fibronectin or fibrinogen binding proteins, decreased binding to the AD skin, but not psoriatic or healthy skin.<sup>108</sup> Scratching by AD also enhances the binding of staphylococcus to the skin by disrupting the skin barrier, and by exposing epidermal and dermal laminin and fibronectin allowing staphylococcus to bind.

### Viral Infections

The importance of viral infections in atopics has been highlighted recently because of the events of 9/11. The last case of smallpox in the United States was in 1949, and the last naturally occurring case in the world was in Somalia in 1977. Routine vaccination of the American public against smallpox stopped in 1972 after the disease was eradicated in the United States.<sup>110</sup> In 1980 the World Health Organization (WHO) announced that small pox had been eradicated from the world, thus eliminating the need for small pox vaccinations worldwide. It is currently estimated that approximately 119 million residents have been born in the United States since the small pox vaccination has been discontinued.<sup>111</sup> With the resurgence of bioterrorism, the issue of vaccination has resurfaced. Currently, any individual with a history of or current active AD, as well as those who have close household contacts to an atopic individual are currently excluded from the small pox vaccination, because of the risk of eczema vaccinatum, which is a serious, life-threatening infection.<sup>112</sup> This complication was recently highlighted in the case of transmission from an active military recruit had received the vaccine three weeks earlier, and transmitted eczema vaccinatum to his two year old son and wife.<sup>113</sup> Conventional treatment with immune globulin and the antiviral drug cidofovir failed. Only through treatment with an investigative drug through SIGA Technologies, called ST-246 did the child survive, highlighting the seriousness of infection with eczema vaccinatum.

Eczema herpeticum is a disseminated herpes simplex virus infection with either HSV 1 or 2, most commonly in atopic individuals.<sup>114</sup> Most infections in ADEH start with a simple labial infection, which then spreads to involve the facial area, and in severe cases spreads over the entire body.<sup>114</sup> Risk factors for ADEH within the atopic population are, higher total serum IgE levels, early age of onset of AD, location of eczema on the head and neck area, and higher sensitization against aeroallergens, especially the yeast *Malessezia sympodialis*.<sup>115</sup>

As mentioned earlier, cathelicidin exhibits antiviral activity against HSV and vaccinia virus, and cathelicidin expression is inversely correlated with serum IgE levels in EH patients.<sup>116</sup> Skin from atopic patients with eczema herpeticum show reduced expression of cathelicidin, and cathelicidin deficient mice show higher levels of HSV-2 replication.<sup>116</sup> Human and mouse

cathelicidin reduce vaccinia virus plaque formation *in vitro*, and CRAMP knockout mice show more vaccinia pox formation than in control mice.<sup>79,116</sup> Vaccinia virus also replicates faster in AD skin explants than in normal or psoriatic skin explants<sup>100</sup> and these explants show a reduced ability to express cathelicidin following stimulation with the vaccinia virus. The mechanism of this inhibition is thought to be through IL-4 and IL-13 inhibiting vaccinia virus mediated induction of cathelicidin through STAT -6.<sup>100</sup>

Plasmacytoid dendritic cells are also thought to play a key role in the antiviral immune response because of their ability to produce high amounts of antiviral type 1 IFN- $\alpha$  and IFN- $\beta$  upon viral infection.. Although the peripheral blood PDC is increased in AD,<sup>117</sup> they have been shown to be depleted in AD skin compared to other inflammatory skin diseases such as psoriasis, contact dermatitis or lupus.<sup>118</sup> The reason for this depletion is by dose-dependent plasmacytoid dendritic cell apoptosis induction caused by IL-4, and potentiated by IL-10.<sup>119</sup>

## CONCLUSION

Many defects in the innate immune system account for the increase in skin infections in atopics. Defects in the pattern recognition receptors have been identified in both the toll receptors and the intracellular PAMP NOD. Low levels of the antimicrobial peptides cathelicidin, HBD-2, and HBD-3 have been observed in lesional skin of atopics. The antimicrobial peptide dermcidin has been shown to be decreased in sweat. And finally, plasmacytoid dendritic cells are depleted in AD skin compared to other inflammatory diseases such as psoriasis, contact dermatitis or lupus. Defects in both the identification of pathogens, and the agents employed to disarm them, account for the increase in infections in atopics. In the future, identification of these defects may allow therapeutic intervention to correct these deficiencies and reduce the incidence of infection in atopic individuals.

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