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The complex biology and contribution of *Staphylococcus aureus* in atopic dermatitis, current and future therapies

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ABSTRACT

Atopic dermatitis (AD) is a complex, chronic inflammatory skin disorder affecting more than 10% of UK children and is a major cause of occupation-related disability. A subset of patients, particularly those with severe AD, are persistently colonised with *Staphylococcus aureus* (*S. aureus*) and exacerbation of disease is commonly associated with this bacterium by virtue of increased inflammation and allergic sensitisation, aggravated by skin barrier defects. Understanding the complex biology of *S. aureus* is an important factor when developing new drugs to combat infection. *S. aureus* generates exoproteins that enable invasion and dissemination within the host skin but can also damage the skin and activate the host immune system. Antibiotics are often used by dermatologists to aid clearance of *S. aureus*; however, these are becoming less effective and chronic usage discouraged with the emergence of multiple antibiotic-resistant strains. New ways to target *S. aureus* using monoclonal antibodies and vaccines are now being developed. This review will attempt to evaluate the key biology of *S. aureus*, current treatment of *S. aureus* infections in atopic dermatitis and recent advances in developing new anti-*S. aureus* therapies that have potential in severe AD.

What's already known about this topic?

- *S. aureus* infections are closely associated with disease exacerbation in patients with atopic dermatitis
- Antibiotic-resistant strains are becoming more commonplace and there is a need for the development of new drugs

What does this study add?

- New therapeutic approaches using monoclonal antibodies are being developed to help combat *S. aureus* infections. These new therapies specifically target the infecting pathogen and do not harm the beneficial microbiome or cause resistance to antibiotics

ATOPIC DERMATITIS AND ASSOCIATION OF STAPHYLOCOCCUS AUREUS

Atopic Dermatitis (AD) is a chronic, relapsing, Th2-polarised inflammatory skin disease that commonly begins in infancy (~ 85% of cases), but can persist or start in adulthood. The disease has a wide clinical spectrum, but is typically characterized by eczematous skin lesions most commonly on the flexural areas and face, pruritus/itch, sleeplessness (often caused by worsening of itching at night), and a predisposition to microbial skin infections, in particular *Staphylococcus aureus* (*S. aureus*)^{1,2}. The precise role of microbial communities in the pathogenesis of AD is incompletely understood although *S. aureus* colonisation, found to be as high as 90% of lesional skin and 55-75% of unaffected skin in AD patients², and reduced bacterial diversity^{3,4} have long been associated with disease flares. As the severity of the lesions increases, so too does the occurrence and number of *S. aureus* isolates recovered from the skin of AD patients compared with healthy controls⁵.

Furthermore, the reported increasing incidence of methicillin-resistant *S. aureus* (MRSA) strains in AD, particularly in paediatric patients, is an alarming development^{6,7}. These recent studies of MRSA prevalence indicate that the AD skin may provide a favourable reservoir for this drug-resistant pathogen and speak to concerns over the repetitive and/or inappropriate administration of antibiotics for the treatment of this disease. Clinically, sites of infection manifest as a yellowish

crusting, confined to lesional areas of the skin (**Figure 1**). Innate immune system abnormalities in AD, including a reduction in anti-microbial peptides (AMPs)⁸, diminished recruitment of neutrophils to the skin and pathogen receptor defects⁹, as well as epidermal barrier abnormalities, all contribute to *S. aureus* colonisation and infection and are not mutually exclusive. Indeed a recent GWAS study identified 10 new loci robustly associated with atopic dermatitis related to autoimmune regulation, but in particular innate signaling and T-cell activation¹⁰. The underlying mechanisms that contribute to colonisation and infection are poorly understood but likely vary according to the patient's genetic predisposition and the environment. This review will discuss the current understanding of *S. aureus* involvement in AD along with current and future therapeutic strategies to modulate or prevent disease exacerbations.

SKIN COLONISATION MECHANISMS OF *S. AUREUS*

Human skin, a complex composite of structural, immunological, nervous and hormonal networks, functions as a physical and chemical barrier and the first line of defence against multiple stresses including wounding and invasion by foreign pathogens. The skin surface has several properties that prevent colonisation and infection with *S. aureus*, including a low temperature and pH to resist microbial growth¹¹. *S. aureus* can exist harmlessly and transiently as a commensal in skin without causing overt disease, with approximately 20% of the world's population being persistent carriers within the nasal cavity¹². However, upon expression of various accessory/virulence factors, *S. aureus* can exert direct effects on keratinocytes to influence the induction and persistence of AD lesions. These virulence factors enable *S. aureus* to adhere to cells and the extracellular matrix (ECM), to evade the host immune response and degrade tissues for nutrition and invasion, dissemination and transmission. Expression of these factors is dependent upon a complex range of global regulatory genes, including *agr*, *sae*, *rot*, and *srr*, thought to act in a time- and population-dependent manner in response to signals received from the external environment and the needs of the bacterium, to drive the internal metabolic machinery¹³.

The first contact of *S. aureus* with the skin to initiate colonisation occurs via well-characterised adherence factors (adhesins). The largest group of these are the microbial surface component recognizing adhesive matrix molecules (MSCRAMMs), which bind prominent ECM components such as fibronectin, fibrinogen, elastin and collagens, and include fibronectin-binding protein (FnBP) A and B, collagen adhesin (Cna), extracellular adhesion protein (Eap)¹⁴ and clumping factor (Clf) A and B proteins^{15,16}. The archetypal cell-wall anchored protein staphylococcal protein A (SpA), well known for its binding to the Fc domain of immunoglobulin G (IgG) and inhibition of opsono-phagocytosis, can also function as an MSCRAMM by mediating attachment to von Willebrand factor, present at sites of endothelial damage¹⁷. The skin of patients with AD has been observed to have increased adherence for *S. aureus*. This is most probably related to the underlying Th2 inflammation since IL-4 induces fibronectin synthesis and plasma exudation of fibrinogen in skin lesions^{18,19}. IL-4 and IL-13 are also known to induce fibronectin production by skin fibroblasts^{20,21}. Moreover, scratching exposes ECM adhesins for *S. aureus* by disturbing the skin barrier¹.

KERATINOCYTE RESPONSE TO *S. AUREUS* INFECTION

Keratinocytes are dynamic cells involved in a highly ordered set of developmental activities, beginning with proliferation and followed by maturation, cornification and shedding²². Keratinocytes perform a dual function in the skin; on one hand, they provide a passive protective barrier through the formation of tight junctions and the stratum corneum²³. On the other, keratinocytes are active participants in innate immunity, orchestrating inflammatory responses to injury or infection through the production of immunomodulatory molecules. *S. aureus* produces multiple virulence factors that facilitate colonisation and dissemination within the skin. However, in doing so, a robust and complex pro-inflammatory response is initiated. In the following section, mechanisms by which the skin epithelium responds to *S. aureus* infection will be described (as summarised in **Figure 2**).

The recognition of pathogens by innate immune cells is mediated by detection of conserved pathogen associated molecular patterns (PAMP) by pattern recognition receptors (PRR), of which one major group comprise the transmembrane toll-like receptors (TLR). Other classes of receptor that may mediate responses to *S. aureus*, such as C-type lectins and peptidoglycan recognition proteins (PGRP), have also been identified^{24,25}. TLR2 primarily mediates cell signalling induced by *S. aureus* and other Gram-positive bacteria, and can form heterodimers with TLR1 and TLR6 to broaden its specificity for triacyl and diacyl lipoproteins, respectively, to enhance responses to *S. aureus* lipoteichoic acid (LTA) and phenol soluble modulins (PSM)^{24,26,27}. PRR are also responsible for responding to endogenous damage associated molecular patterns (DAMP), generated in the setting of tissue injury or damage²⁸. As it is known that *S. aureus* can be internalised by professional and non-professional phagocytes, including human keratinocytes²⁹⁻³¹, intracellular *S. aureus* PAMPs may also activate the nucleotide-binding oligomerisation domain-containing protein (NOD) and NOD-like receptor (NLR) family of cytoplasmic pathogen sensors^{9,14,32}. The potential clinical importance in AD of NOD2, specific for the muramyl-dipeptide (MDP) derived from Staphylococcal peptidoglycan (PGN) and functionally expressed by keratinocytes³³, is revealed by an association between AD and polymorphisms in the NOD2 gene^{34,35}. Furthermore, α -toxin facilitates NOD2 dependent recognition of MDP, possibly by interfering with phagosomal integrity, and NOD2^{-/-} mice exhibit increased susceptibility to subcutaneous *S. aureus* infection^{36,37}.

Activation of the NLR Family, Pyrin Domain Containing 3 (NLRP3) inflammasome is achieved by various microbial as well as endogenous danger signals and is implicated in the sensing of *S. aureus*³⁸. The proximal steps in NLRP3 activation are not well understood but, given the plethora of activating signals, triggering is likely elicited through an intermediate cellular signal and requires upregulation of NLRP3 and pro-IL-1 β expression by microbial ligands or endogenous cytokines in a priming step³⁸. *S. aureus* can activate NLRP3 through its secretion of pore-forming toxins, notably α -toxin²⁹. It has been proposed that pore formation can trigger K⁺ efflux, release of cathepsins and other factors from ruptured lysosomes, damage to mitochondria and the production of reactive oxygen species (ROS) to activate the NLRP3 inflammasome^{32,38,39}. Extracellular ATP released at sites of cellular injury or necrosis may also function in an autocrine manner to activate the purinergic ATP-gated P2X7 receptor. P2X7 acts as a cation channel to induce the release of intracellular potassium and may additionally serve as a conduit to deliver microbial molecules to the host cytosol³².

After establishing contact with keratinocytes, *S. aureus* can secrete a number of exoproteins, including enzymes with cell damaging and immune activating properties, such as nucleases, lipases, proteases and collagenases⁴⁰, and exotoxins with direct cytolytic activity that include the prototypic hemolysins or toxins (α , β , γ and δ), leukocidin and panton-valentine leukocidin (PVL). The best studied of the *S. aureus* toxins is α -toxin (α -hemolysin) which is secreted as a water-soluble

monomer, binds its receptor A disintegrin and metalloprotease 10 (ADAM10) and oligomerises into a cylindrical heptamer to form a transmembrane β -barrel⁴¹. Pore formation causes loss of membrane integrity, activation of stress-signalling pathways, leakage of cell contents, alterations in ion gradients and eventually cell lysis. Human cells vary in their susceptibility to α -toxin which likely reflects ADAM10 expression levels, the intracellular signalling events elicited in different cell types and differential capability of host cells to remove α -toxin pores. This is evident in keratinocytes, which can repair toxin-induced membrane injury through sequential endocytosis from the membrane and exocytosis of the toxin in so-called 'toxosomes'⁴². However, in AD, the Th2 cytokines IL-4 and IL-13 can augment α -toxin-induced lethality of keratinocytes by decreasing levels of sphingomyelinase, which normally cleaves the α -toxin receptor sphingomyelin⁴³.

In addition to cytolytic toxins, *S. aureus* produces toxic shock syndrome toxin 1 (TSST-1) and the well-characterised staphylococcal enterotoxins (SE-A, B, C, D, E and G) and enterotoxin-like (SE-I) exotoxins (H, I and J-X) as well as the exfoliative toxins (ETA and ETB). TSST-1 and SEs share the property of superantigenicity. This is defined as the stimulation of T-cell proliferation through cross-bridging of the variable part of the T cell receptor β chain (V β -TCR) with major histocompatibility complex class II (MHC-II) molecules on antigen-presenting cells (APC), without the requirement for antigenic peptide presentation, and can stimulate a 'cytokine storm'⁴⁴. Whilst no evidence of superantigens driving a "cytokine storm" has been described in AD, there is much evidence describing a potential role. Superantigens, including SEB, have been shown to upregulate the skin homing receptor, cutaneous lymphocyte-associated antigen (CLA) on T cells⁴⁵. Thus it is possible superantigens could increase recruitment of T cells to the skin. Superantigen specific IgE can also be detected in AD patients at a higher level than seen in healthy controls and thus a potential role in mast cell activation exists⁴⁶. This elevated IgE response also highlights an inappropriate Th2 type response to this bacteria and thus ineffective control of infection.

S. aureus also produces a number of extracellular proteases with pleiotropic roles in pathogenesis, and among these the serine proteases, such as a serine glutamyl endopeptidase (SspA; also referred to as the V8 protease), cysteine proteases (e.g. staphopain) and metalloproteases (e.g. aureolysin; Aur) are the most abundant. They are instrumental both in host damage and microbial adaptation to the host through degradation of virulence factors, and provide a rapid response to environmental signals⁴⁷.

Staphylococcal protein A causes increased serum IL-18 and circulating IgE following cutaneous application in mice⁴⁸. Furthermore, when incubated with keratinocytes, SpA stimulates the production of TNF- α ⁴⁹, as well as IL-8 and COX-2 via TNFR1-mediated NF κ B and AP-1 activation; this is of relevance in AD, where >85% of tested strains secrete significant amounts of SpA⁵⁰. Activation of TLR2 signalling by PGN from *S. aureus* can induce LL-37 and VEGF expression in keratinocytes, which has been suggested to stimulate their proliferation and induce angiogenesis to provide nutrients and oxygen in the skin⁵¹. PGN has also been shown to stimulate the expression and production of GM-CSF, which involves activation of p38 MAPK and ERK, as well as the expression or production of other mediators thought to contribute to skin disorders, such as RANTES, TNF- α , IL-6, IL-8, MCP-1 and ICAM-1. GM-CSF is essential for the survival, differentiation and maturation of dendritic and Langerhans cells⁵². It is thought to shift the immune response to a Th2-dominant type through its effects on APCs, and also has mitogenic effects on keratinocytes to induce hypertrophy⁵².

Despite showing no differences in TLR2 or 6 expression, it has been demonstrated that keratinocytes from AD patients have an intrinsically reduced capacity to secrete IL-6, IL-8, CCL-20 and MMP-9 upon TLR2 stimulation (with LTA and PGN) compared to healthy controls⁵³. NLRP3 and Caspase-1 are

down-regulated in lesional AD skin compared to healthy skin, and these effects can be recapitulated by treating keratinocytes with a combination of Th2 cytokines (IL-4, IL-5 and IL-13). Moreover, α -toxin down-regulated NLRP3, ASC and IL-1 β expression, pointing to a negative feedback loop, and could explain how the Th2 milieu and *S. aureus* colonisation can contribute to chronic skin inflammation in AD⁵⁴.

Attempts by numerous groups to characterise *S. aureus* isolates from AD skin have been largely unsuccessful and may, in part, be attributed to the diversity of patient cohorts examined⁵⁵. The supposition that *S. aureus* in AD originates from the patient's own flora, together with the observation that geographically distinct *S. aureus* strains have different distributions of virulence genes^{56,57}, make the task of correlating *S. aureus* genotype with clinical severity a difficult one. The fact that *S. aureus* is also endowed with many features enabling resistance to immune detection and destruction explain its success in establishing a foothold in AD, and underscore the overwhelming challenges faced in containing it.

CURRENT CLINICAL PRACTICE FOR TREATMENT OF *S. AUREUS* IN AD

It is common clinical practice to treat patients with evident *S. aureus* skin infections with topical or systemic antibiotics. Painful, oozing or crusting lesions, usually with an asymmetrical distribution, normally disappear within days of treatment with systemic antibiotics. However, it is the balance between colonization and infection that is resulting in the discussion: "to treat or not to treat? (with antibiotics)". From a clinical point of view, the differentiation between colonization and infection can be difficult, and there is no absolute measure for this differentiation. It has been shown that colonization density can reach up to 10⁷ colony-forming units/cm² without clinical signs of infection⁵⁸.

As described extensively in the previous sections, multiple layers of evidence have suggested important roles for *S. aureus* in the pathogenesis of AD. Together with the observation that approximately 90% of AD patients are colonized with *S. aureus* compared to a much smaller percentage of normal controls, this suggests a relationship between colonization and disease. Whether the emergence of *S. aureus* is causal to AD, or just a consequence of chronic inflammation, is still a matter of debate. Antimicrobial treatment, both topical and systemic, has been shown to reduce *S. aureus* numbers⁶²⁻⁶⁵, however this has not translated into clear clinical benefit (decrease in AD symptoms) using current therapeutic approaches^{59,60}. It should be noted that these studies comprised small patient numbers, were poorly reported and thus may not have shown the anticipated benefit^{59,60}. Complete *S. aureus* eradication may be required to deliver improvement in AD symptoms. Indeed, it has recently been suggested that antibiotic cocktails might be necessary to successfully target skin colonizing *S. aureus*, as is done for *Helicobacter pylori* infections of the stomach⁶¹.

Furthermore, it was found that patients treated with antibiotics quickly become re-colonized, often with the same toxin-secreting organism⁶². Long term treatment would be indicated to prevent re-colonization, though not advisable due to the inherent risk of inducing antibiotic resistance. Invasion of host cells in the skin is also a proposed mechanism by which *S. aureus* escapes antibiotic encounter. The existence of *S. aureus* small colony variants (SCVs), associated with relapsing and persistent infections in osteomyelitis³¹ and cystic fibrosis⁶⁶, and implicated in the failure of antibiotic treatment for a case of Darier's disease⁶⁷, support a hypothesis that the keratinocyte intracellular niche could feasibly serve as a *S. aureus* reservoir for chronic and relapsing infections in AD.

Other anti-staphylococcal treatments such as dilute bleach baths⁶⁸, silver-impregnated textiles^{69,70} and disinfectants⁷¹ may be effective in reducing bacterial load on the skin and recurrent infections, but high quality evidence for these interventions is currently lacking. Likewise, therapies that can interfere with factors governing *S. aureus* clearance and survival, to reduce bacterial dominance and recurrence, and recalibrate the microbiome, may be beneficial but are poorly studied.

New drugs, inducing long term reduction/elimination of *S. aureus* (colonization), but not antibiotic resistance, will elucidate the role of *S. aureus* in AD.

FUTURE THERAPEUTIC APPROACHES TO TREAT *S. AUREUS* INFECTION

As highlighted above, *S. aureus* infections are problematic and can be difficult to treat. The current antibiotic-resistance epidemic could return us into a pre-antibiotic era, and has been fuelled by decades of empiric broad-spectrum antibiotic therapy along with the use of antibiotics to promote livestock growth. In addition to promoting the spread of antibiotic resistance, it has become evident that broad-spectrum antibiotic use damages the healthy microbiome (dysbiosis) and has been linked to increased susceptibility to *Clostridium difficile* infections and a variety of metabolic disorders^{72,73}. Consequently, there is a need to develop pathogen-specific, precision therapies that target only the infecting pathogen and do not harm the beneficial microbiome or cause resistance to antibiotics. Such therapies aim to promote opsonophagocytic killing, or neutralize key virulence determinants expressed by the infecting bacteria. Whilst *S. aureus* colonisation itself does not present clinically as a problem, indeed healthy individuals are often colonised with no adverse clinical effect, it does still represent a bacterial reservoir for future infections. Therefore, prophylactic treatment with new, non-antibiotic therapeutic agents aimed at eliminating *S. aureus* completely, or at least inhibiting growth, could prevent infections before they occur.

Because of the clinical and economic burden of *S. aureus*-associated disease on the healthcare system, significant effort has been invested into researching and developing alternative strategies specifically targeting *S. aureus* infections such as therapeutic monoclonal antibodies (mAbs), vaccines and even *S. aureus*-specific phage lysins. To date, vaccine and mAb-based approaches targeting single *S. aureus* surface antigens have been unsuccessful in clinical testing⁷⁴. There may be many reasons for these failures including only targeting a single bacterial antigen and the lack of approaches targeting key staphylococcal toxins, which have led to new anti-toxins and multi-antigen vaccine formulations. As described earlier, the pore-forming toxin, α -toxin is a key virulence determinant in *S. aureus* skin disease⁷⁵. In a recent report, it was shown that high anti- α -toxin antibody titres correlate with reduced recurrence of *S. aureus* skin infections⁷⁶. In fact, monoclonal antibodies (mAbs) and vaccines targeting α -toxin have been reported to reduce the damage associated with *S. aureus* skin infections in preclinical disease models^{77,78}. Therefore, providing a high neutralizing anti- α -toxin IgG titre by vaccination or monoclonal antibody (mAb) therapy to AD patients colonized with *S. aureus* could reduce the incidence of flares or severity of disease. One such mAb MEDI4893, which is currently in clinical testing for the prevention of *S. aureus* pneumonia, has been shown to protect against serious *S. aureus* skin infection in mice but has yet to be tested in preclinical AD models^{79,80}. Another mAb, ASN100, neutralizes not only α -toxin but 4 additional *S. aureus* toxins (LukED, LukSF and HlgAB/CB)⁸¹; such molecules could hold promise in AD. Non-antibiotic small molecule inhibitors of α -toxin or its receptor, ADAM-10, have also been reported to reduce the severity of *S. aureus* disease in animals^{82,83}. In addition to neutralizing toxins, there are also mAbs and vaccines in development targeting one or more *S. aureus* surface components. Such approaches could neutralize virulence determinants and also target the bacteria for opsonophagocytic killing by immune cells. SA4ag and 4C-Staph are two vaccines comprised of

multiple antigens; SA4ag consists solely of *S. aureus* surface antigens whereas 4C-Staph includes surface antigens and α -toxin^{84,85}. These vaccines look encouraging in some preclinical models but there are no reports of them having activity in *S. aureus* skin infections and they have yet to be tested in preclinical models of AD.

Whilst use of biologics provides an exciting approach to control *S. aureus* colonisation and infection, usage may come with significant cost. Therefore, much work has been conducted investigating alternative treatments that may be more cost effective. More recent approaches have been aimed at boosting the innate immune system, by increasing AMP production by keratinocytes using adenovirus, and using cationic steroids such as ceragenins to mimic naturally occurring AMPs; these compounds have the added advantage of human protease resistance, prolonging their half-life, and could be marketed as topical broad-spectrum anti-bacterials^{86,87}. Vitamin D may also be important for AMP production, supported by the results of a trial with oral vitamin D in AD patients showing an induction of cathelicidin production⁸⁸, the finding that skin wounding or stimulation of keratinocytes leads to increased cathelicidin expression via a vitamin D-dependent pathway⁸⁹, and the observation that vitamin D deficiency carries an increased risk of MRSA carriage⁹⁰. Probiotics might also help to restore a healthy microbiome of commensal bacteria, which are known to possess immunomodulatory properties, but have not proven successful for the treatment of AD thus far and are still under investigation^{91,92}. Bleach baths can be used for patients with moderate to severe AD and clinical signs of secondary bacterial infection, however this is not routinely recommended by dermatologists⁶⁸. Furthermore, the foundation for novel strategies, aimed at restoring molecular mechanisms in the epidermis to normalise skin microbiota (e.g. by restoring EGFR signalling), is provided by observations that eczematous inflammation together with dysbiotic changes and the emergence of *S. aureus* prominence follow the genetic ablation of *ADAM17* and, to a less extent, *EGFR* in mice, which mimics *ADAM17* deficiency in humans⁹³. Certainly, host factors that govern *S. aureus* clearance and survival are poorly studied, and are therefore a rich area for future research and could lead to development of new therapeutic approaches to control *S. aureus*. Another investigative approach to treat *S. aureus* infections is the use of engineered phage lysins. These lysins, which originated from bacteriophages, are pathogen-specific and kill bacteria by cleaving bonds in the cell wall peptidoglycan⁹⁴. These molecules have been demonstrated to be potent antibacterial agents in vitro and to effectively treat disease in preclinical disease models when delivered systemically and topically, an approach of particular interest in atopic dermatitis⁹⁵. Such recombinant phage lysins may therefore be an effective alternative to broad spectrum anti-bacterial therapy.

CONCLUSIONS

S. aureus has evolved to successfully co-exist with its host organism; however, under certain conditions this non-harmful relationship breaks down. In patients with AD, recurrent infections with *S. aureus* are a significant problem contributing to disease flare, driving both tissue damage and inflammation (**Figure 3**). Current therapy is reactive, but management should include early and proactive intervention with effective, continuous control of *S. aureus* colonisation. With antibiotic-resistant strains becoming more commonplace in AD⁹⁶ the development of new drugs to either prevent or treat *S. aureus* associated infections is a priority for the pharmaceutical industry to improve the outcome and quality of life for patients.

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Figure Legends:

Figure 1: *S. aureus* infection is a common feature of moderate to severe AD. Infections are mostly confined to lesional areas of skin and form a yellowish crusting (black arrows).

Figure 2: Recognition of *S. aureus* by pattern recognition receptors on the surface of keratinocytes can drive a robust inflammatory response. *S. aureus* pore-forming exoproteins such as α -toxin can also activate keratinocytes or even cause cell death.

Figure 3: Overview of mechanisms by which *S. aureus* (●) contributes to AD pathology. 1. *S. aureus* releases numerous cytolytic mediators that can cause keratinocyte lysis, including α -toxin, which aid bacterial dissemination. 2. Keratinocytes in response to *S. aureus* invasion produce anti-microbial peptides (AMP) as part of the innate immune response. 3. Keratinocytes produce a broad spectrum of pro-inflammatory cytokines and chemokines that elicit an immune response. 4. Multiple cell types are recruited to skin lesions in response to *S. aureus* infection including Th1, Th17, Th22, macrophage (Mo) and inflammatory dendritic cells (iDC). Th2 cytokines IL-4 and IL-13 can inhibit AMP production and reduce innate anti-*S. aureus* response. 5. Damage to epidermal integrity increases allergen (●) entry and facilitates increased antigen presentation by Langerhans Cells (LC), driving adaptive immune responses.

FIGURE 1



FIGURE 2

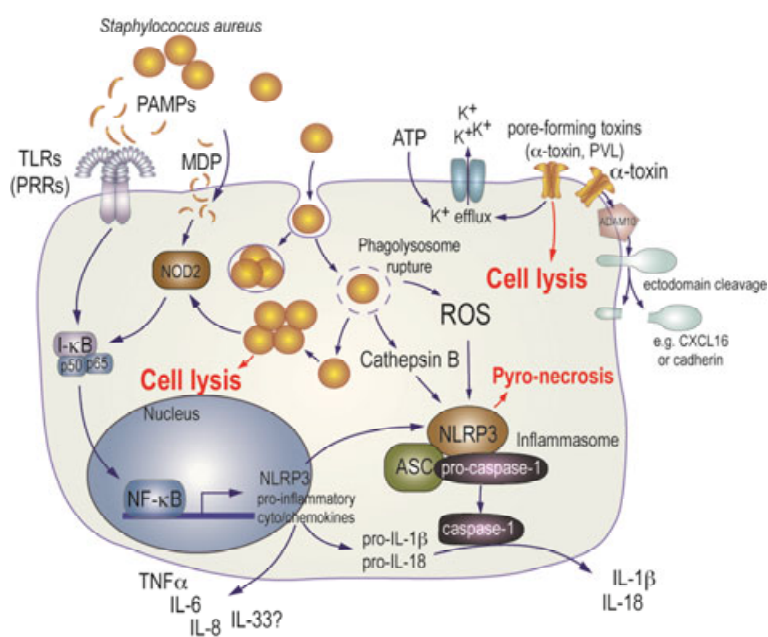


FIGURE 3

