Atopic Dermatitis

Understanding the role of innate immune function

By Aoife Earls MSc, ND

Atopic dermatitis (AD) or eczema is an incredibly difficult disorder to treat due to its wide heterogeneity. There are genetic and immune components to the disorder including: induction of immunoglobulin E antibody production through abnormal T cell regulation with dominant Th2 phenotypes, secondary microbial infections with a disrupted epidermal barrier, reactivity to environmental and food allergies, and increased sensitivity to stress. This article explores the relationship of AD to the innate immune system, and the ability of naturopathic medicine to support reduction of AD severity in afflicted individuals.

PATHOPHYSIOLOGY

Hallmark characteristics of AD include skin barrier disruption and inflammation associated with a chronic itching-scratching cycle, and more importantly, an immune system dysfunction. Clinically, skin barrier disruption presents as eczematous lesions with acute (oozing, crusted, eroded vesicles or papules on erythematous plaques), sub-acute (thick and excoriated plaques), and chronic (lichenified, slightly pigmented, excoriated plaques) forms. Xerosis (severe dry skin) and a lowered threshold for itching, including enhanced trans-epidermal water loss lead to reduced quality of life, as pruritus tends to worsen during the night reducing sleep quality (Bieber 2010, Madison 2003). Disruption of the epidermis from chronic scratching enhances susceptibility to frequent bacterial and viral skin infections (Cho 2001). Approximately 80–100% of AD patients are colonized with Staphylococcus aureus (S. aureus) even on segments of skin not actively inflamed as compared with healthy control subjects (Breuer 2002, Hauser 1985).

Evidence suggests that immune system dysfunction is the source of this skin barrier disruption. A predominant systemic Th2 imbalance with increased IgE levels is widely accepted in the pathogenesis of atopic diseases (Ong 2006), including the production of Th2-mediated cytokines, such as interleukins (IL) 4, 5, and 13 (Bieber 2010). IL-4 and IL-13 are implicated in the initial phase of tissue inflammation that continues in AD (Bieber 2010). IgE auto-reactivity can appears very early (during the first year of life) and is associated with flares in AD, although not all eczema has been previously linked to IgE-sensitized forms (Bieber 2010).

Aoife Earls MSc ND
River Oaks Chiropractic and Wellness Centre
478 Dundas Street West, Unit 6
Oakville ON L6H 6Y3
www.riveroakswellness.com

Wellpath Clinic
170 Bloor Street West, Suite 1106
Toronto ON M4N
www.wellpathclinic.com

THE INNATE IMMUNE SYSTEM IN ATOPIC DERMATITIS (ECZEMA)

Foreign microbes are detected through pattern recognition receptors (PRR), including specific PRR called toll-like receptors (TLR). Antimicrobial peptides (AMP) are produced in response to foreign invaders binding to PRR and TLR, and form not only a shield on the skin surface but also initiate a multitude of components of the innate and adaptive immune system (Neibur 2010, Schauber 2008). AMP like beta-defensins (HBD- 2 and HBD-3) and cathelicidin proteins are peptides that have antibiotic activity against bacteria, viruses, fungi, and protozoa. They can be found in the paneth cells in the small intestine, in the lung, and in the skin.

Not surprisingly, cathelicidins and B-defensins are deficient in patients with AD (Schauber 2008). Deficiencies in antimicrobial peptides (AMPs) and the barrier proteins observed in the skin of patients with AD may be due, in part, to the over-expression of Th2 cytokines such as IL-4 and IL-13 (Howell 2007, Ong 2006). It has been found that controlling the cytokine flood of IL-4 and IL-13 does improve the activity of AMP, and thus modulates the population of S. aureus found on the skin (Kisich 2008). IL-4 is also involved in the up-regulation of IgE receptors on monocytes, which can skew immune responses toward a Th2 response (Ong & Leung 2006). Supporting the up-regulation of AMP (specifically defensins and cathelicidins) is now becoming a focus for AD therapy, with hopes that S. aureus colonization can be decreased with decreased Th2 phenotypic dominance (Cardona 2006).

CONVENTIONAL TREATMENT STRATEGIES

To date, much of the focus on AD has remained on preserving the skin barrier. Moisturizing and conserving water preservation on the surface of the skin are emphasized, and the uses of cortisone ointments have been used to suppress the active inflammation from chronic scratching (Bieber 2010). However, corticosteroids worsen lichenification and weaken the skin, making it more susceptible to infection by suppression of the immune system and hyperactivity of the Th2 components (Baker 2006). Recently, the topical calcineurin inhibitors pimecrolimus cream 1% (Elidel ®) and tacrolimus ointment 0.03% and 0.1% (Protopic ®) exhibit a more selective mechanism of action (Hultsch 2005). Tacrolimus and pimecrolimus inhibit calcineurin, which affects the release of inflammatory cytokines and T-cell proliferation (Berman 2003).

Tacrolimus, shown to improve quality of life and exhibit superior efficacy relative to standard corticosteroids, has been used as a cost-effective alternative despite possible carcinogenesis (Poole 2010). Treatment with calcineurin inhibitors has also been found to reduce S. aureus on the skin indirectly through controlling the inflammatory response (Niebuhr 2010).

NATUROPATHIC TREATMENT CONSIDERATIONS

With the knowledge that pattern recognition receptors on the skin surface are our primary line of defence and interface with pro-inflammatory cytokines, naturopathic medicine has a key role in the support and strengthening of these host defences.

PROBIOTIC THERAPY

Colonization of the gastrointestinal tract begins at birth with microbes mostly from the mother's vaginal canal and gastrointestinal tract such as bifidobacteria and lactobacillus (Ozdemir 2010). The immune system itself is directed towards a Th2 phenotype and the innate immune system. As the infant matures, immunity is driven to more Th1 affinity or the development of the adaptive immune system. The shift from Th2 to Th1 phenotypes is important, as Th2 phenotypes are associated with the development of allergy (Ozdemir 2010). Differences in the bacterial colonization of the gut have been reported in children with AD; Enterococci and Bifidobacteria have been found to be reduced, and Clostridia and Staphylococcus aureus numbers increased (Watanabe 2003). These changes have been attributed, at least in part, to a frequent use of antibiotics, which has consistently been shown to markedly increase the risk of developing AD (Baker 2006).

The landmark study by Kalliomaki and colleagues was the first report that the frequency of AD in neonates treated with Lactobacillus rhamnosus GG was half that of the placebo group (Kalliomaki 2007). Current research is varied for the use of probiotics for AD in several settings; prenatal probiotic supplementation by mothers with AD history or atopic history; post-natal consumption of probiotic strains in mothers and babies; and children with current AD. The Severity Scoring of Atopic Dermatitis (SCORAD), is the standard assessment tool in all RCT trials evaluating the efficacy of probiotic use and is an accurate subjective tool of AD status (Vourch-Jourdain 2009).

Several reviews have been conducted, comparing multiple RCT's (Ozdemir 2010, Tang 2009, van der Aa 2010) as well as a meta-analysis of RCT's (Lee 2008). The most common strains utilized include Lactobacillus rhamnosus, Lactobacillus casei and Lactobacillus reuteri. A meta-

analysis of 6 prevention and 4 treatment clinical trials demonstrated a 61% reduced risk of AD associated with the use of prenatal and/or postnatal probiotics (Lee 2008). Lactobacillus GG was the primary probiotic used. Changes in the Th2 phenotype of the immune system appear significant for AD prevention, again with added benefit conferred by probiotic usage prenatally in mothers with IgE-sensitized immune systems (Betsi 2008).

All RCT reviews and meta analyses concede that significant findings need to be further explored due to many inconsistencies between each investigation, including the use of effective bacterial species/strains, optimal dosing of each strain, whether there may be added benefit with synbiotics (a prebiotic in addition to the use of a probiotic), the optimal timing for intervention (prenatally, post-natal and duration in childhood), and patient populations that would gain the most benefit (preventative AD or to relieve current symptomatic AD in children or adults) (Lee 2008).

FISH OIL

The fat layer, the stratum corneum, creates a barrier that helps to keep water within the body and prevent the entrance of pathogens and allergens (Choi 2005). The major lipids in the stratum corneum are ceramides (50% by mass), fatty acids (10–20% by mass), and cholesterol (25% by mass) (De Benedetto 2009). Patients with AD have reduced levels of all of the above (Imokawa 2001). Stress may aggravate this phenomena by the production of endogenous glucocorticoids, which suppresses epidermal lipid production (Choi 2005). Presumably, increased polyunsaturated fatty acids (PUFA) through diet should improve the lipid barrier for individuals suffering with AD, as PUFAs play key roles in membrane fluidity and signalling (Calder 2009).

The ability of omega-3 fish oils to reduce inflammation through a shift of enzymes in the arachidonic acid pathway has been well- documented (Calder 2009). PUFA presence in the arachidonic acid pathway, and specifically EPA and DHA components of PUFA, have the ability to down-regulate COX-2 and prostaglandin production which are molecules up-regulated in inflammation and increased Th2 immune responses (Calder 2006). A recent systematic review examined fish consumption during pregnancy and subsequent risk in offspring of AD, demonstrating important inverse correlations (Kremmyda 2009). Synthesis and uptake of cholesterol and fatty acids with the enzymes ATPCitrate lyase, Acyl-CoA synthase, HMGCoA synthetase and HMG-CoA reductase as well as genes encoding PUFA pathway have all been found to be down-regulated in AD (Kremmyda 2009). Hence, increased consumption of fish- derived omega-3 fatty acids (EPA and DHA) through diet could influence chronic inflammation seen in AD.

Signalling with the innate immune system is also theorized to be influenced by PUFA (Lee 2003). A randomized controlled trial (n=8) exposed blood monocytes in vitro post-consumption of 9g fish oil daily to lipopolysaccharide (LPS), components of a bacterial cell wall which typically activate toll-like receptors (TLR) (Lee 2003). A down-regulation of COX-2 expression was specific. If synthesis of PUFA is down-regulated in AD, in turn, the ability to provide antimicrobial defence is that much more affected in deficiency which might explain increased susceptibility to infection in AD.

IgG-MEDIATED FOOD INTOLERANCES VS. IgE-MEDIATED FOOD ALLERGY

There is a significant discrepancy with the relationship of food sensitivities and/or allergies with AD severity. Foods thought to aggravate AD include wheat and wheat gluten, dairy products, soy, nut families, high acid foods (citrus fruits, tomatoes, coffee) (Greenhawt 2010). Current tests for food sensitivity involve skin-based IgE reactions to foods, which involve a skin scratch test performed by an allergist, and rarely, an IgE serum test. Research is incredibly varied and focuses on the IgE skin-immediate reactivity to food with little attention to IgG Type III delayed-type hypersensitivity reaction to foods.

Cytokine production of total and food-specific IgE has been correlated with higher levels of IgG1 and IgG4 to peanut, milk, and egg when comparing children with a history of atopy to non-atopic children or adults ($p<0.05$). This outcome is consistent with a Th2 cytokine response to sensitizing antigens. Antigen-specific IgG subclasses and IgE antibodies were compared with intracellular T cell cytokine changes to sensitizing antigens in 23 children with multiple food allergies and 20 healthy controls. Elevated allergen-specific IgG subclass antibodies in sensitized children correlated with total IgE levels ($p \leq 0.05$) across all three food allergen groups tested (Scott-Taylor 2010). Thus, with an atopic profile IgG and IgE have significant connection to one another.

VITAMIN D

Upon skin injury or bacterial infection there is a local activation of vitamin D3 to induce AMP activation, and specifically cathelicidin expression and function (Hata 2008). In atopic dermatitis, there is evidence that this signalling may be altered due to the high concentration of Th2 cytokines. It has been found that Th2 cytokines such as IL-4 and 13 suppress the induction of AMPs and contribute to a disturbed cutaneous antimicrobial response. However, in vitro administration of 1,25D3

increases cathelicidin expression and antimicrobial activity in keratinocytes (Schauber 2008). Administration of 4000 IU daily orally of vitamin D3 (cholecalciferol) for 21 days (n=14) achieved statistically significant improvement of AD skin lesion severity ($p < 0.01$), and induced cathelicidin production (Hata 2008). In theory, increased availablility of vitamin D would improve healing of AD lesions (Hata 2008, Schrauber 2007).

CONCLUSION

Quality of life may be directly affected by improving our understanding of innate immunity in atopic dermatitis and other atopic conditions. Discovery and elimination of food sensitivities, probiotics, fish oil and vitamin D have demonstrated direct impact on aspects of innate immunity involved in AD, as well as clinical utility in the management of the disorder.

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