Pathogenesis of Atopic Dermatitis in Singapore

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Atopic dermatitis (AD) commonly known as eczema is a dry, itchy condition more frequently present at skin flexures (Williams, 2005; Cork et al., 2009). In 1994, surveys conducted in over 30 schools in Singapore showed the prevalence of AD at 12% which later grew to 20.8% in 1999 (Goh et al., 1996; Tay et al., 2002). Increasing prevalence rates were seen not only in Singapore but in many other developed countries around the world. These increasing and diverse trends seen across the globe indicated an active role of environment and not just genetics in the pathogenesis of AD. Thus, to study such common diseases without the effect of confounding factors of environment and anthropological-origin, locale and ethnic specific studies are usually conducted.

In a revision of allergy-related nomenclature, the World Allergy Organisation in 2003 termed eczema as an umbrella term for dermatitis involving genetically determined skin barrier defects (Johansson et al., 2004). The need for a standardised definition involving genetic skin barrier defects arose when an alternative hypothesis of the pathogenesis of AD started gaining momentum in early 1990s. Up until then, the classical cause for AD was thought to be atopy alone. As the name suggests, the disease has atopic manifestation and was long believed to be the only cause for it. Literature around that time repeatedly showed associations of atopic markers to AD. The associations were at the genetic (Leung et al., 1986) and protein levels (Hanifin, 1986) of key Th2 pathway elements and increased IgE levels. However, in 1990 Hideoki Ogawa in his address at the 15th Annual Meeting of Japanese Society for Investigative Dermatology was the very first to hypothesize the importance of a dysfunctional barrier in the pathogenesis of AD. He along with Takashi Yoshiike was the first to publish this alternative hypothesis integrating barrier dysfunction and atopy as key players to the pathogenesis of AD (Ogawa et al. 1992). Following this, Alain Taeib and others started describing AD in this new perspective which lead to a wider acceptance of this alternative theory (Taieb, 1999).

Skin is the largest organ separating us from the external environment. It forms the first line of defence by providing not just a physical but also a more complex chemical and biological barrier. These defensive functions include a physical permeability barrier, which retards transepidermal evaporative water loss—allowing survival in a desiccating external environment; biological
barrier, which by encouraging colonization of non-pathogenic 'normal' flora resists growth of microbial pathogens (Elias et al., 2009). Thus, an intact-uncompromised epidermis is a prerequisite for the skin to function as a barrier.

The skin forms a barrier much like a wall as has been visualised by Peter Elias and Micheal Cork and illustrated below (Figure 1). The cells (corneocytes) can be considered as bricks forming a wall which are held together by junction proteins (corneodesmosomes). The space in-between is filled with lipid lamellae similar to cement which helps caulk the gaps to prevent water loss and entry of allergens. In the process of squamation and de-squamation, the corneocytes (skin cells) proliferate from the lower layers, differentiating and eventually dying as they proceed to the upper layers. This entire process is regulated by a fine balance of proteases which break the connections that enable the dead cells to slough and fall off. The proteases are regulated by their respective inhibitors which are in-turn regulated by the pH differences of the various layers of the skin they lie in. (Elias et al., 2008). Thus, a dysfunctional barrier or an aberration in any of the processes involved in maintaining this balance can form a potential entry point for allergens and pathogens.

A/P Chew Fook Tim's Allergy and Molecular Immunology lab in National University of Singapore (NUS) had been focused on identifying and characterizing various classes of allergens. With the passage of time the lab gradually shifted to the genetics of allergies and allergic diseases and the lab began to collect a study population from NUS and a few collaborating hospitals. The sample size of which has now grown to over 7000. The lab conducted two genome-wide association studies to find novel associations to asthma and allergic rhinitis (Ramani et al., 2011). With me joining the lab in early 2009, the lab diversified its interest into the third commonly studied atopic disease – atopic dermatitis. At a prevalence of a mere 10% in the study population, candidate gene study was adopted rather than genome wide screens. With barrier dysfunction as the hypothesis for my project, protein differences in the skin were assayed to give more insight into the pathogenesis of the disease. Proteins selected for studies were based on the different mechanisms by which they helped maintain the barrier. These included but were not restricted to—proteases, protease inhibitors, junction proteins, anti-microbial peptides, differentiation markers. The protein study similar to the genetic associations was conducted in 2 stages—screening and a later validation of the significant candidates. To gain a deeper insight into the observed

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Figure 1: Graphical representation of the stratum corneum as a barrier (Adapted from Cork et al., 2006.)
differences, genetic data was analyzed to check the variability in the gene codes for the observed differences in protein levels. However, not all observed changes in proteins can be ascribed to genetic variability, as the protein levels could be a result of many epigenetic and protein interactions. The lab is currently functionally characterizing the genetic and protein leads.

There are scores of papers on genetic associations and protein biomarkers for diseases. However, very few of them actually bridge the link between the two. Even rarer is the further characterization of these associations to the disease phenotypes. But, A/P Chew Fook Tim’s lab is one of the few labs which work towards narrowing the associations to the causative factors and then to the effect which eventually plays a part in disease pathogenesis. As more causal elements get identified, it will form the basis for diagnosis and eventual targeted therapies for common diseases. Thus, the lab in the true sense is a translational research facility which caters to the basic sciences and to the clinical pathologies of diseases.

References

About the Author
Bani K. Suri is pursuing her doctoral studies at National University of Singapore under the aegis of A/P Chew Fook Tim. She has done her Bachelor’s and Master’s from University of Mumbai, India. She worked in the R&D of a pharmaceutical company before enrolling for the PhD program. She had been the chairperson for organizing an International Graduate Congress for the Department of Biological Sciences in 2011.