A Brief History of Asthma and Its Mechanisms to Modern Concepts of Disease Pathogenesis

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The original concept of asthma being primarily a disease of airways smooth muscle drove the development of bronchodilator drugs. However when it was realised that airway inflammation underpinned the disordered airway function, this gave way to the development of controller therapies such as inhaled cromones and corticosteroids. More recently the discovery of complex interconnecting cytokine and chemokine networks has stimulated the development of biologics with varying success. With the recognition that airway wall "remodelling" is present early in asthma inception and is in part driven by aberrant epithelial-mesenchymal communication both genetic and environmental factors beyond allergen exposure such as virus infection and air pollution are being seen as being increasingly important not only in asthma exacerbations but in the origins of asthma and its evolution into different sub-phenotypes. This brings us round full circle to once again considering that the origins of asthma lie in defects in the formed elements of the airway; the epithelium, smooth muscle, and vasculature. Over the last 25 years Professor You Young Kim has engaged in the exciting discovery science of allergy and asthma and has made an enormous contribution in bringing Korea to the forefront of disease management and research, a position that both he and his colleagues can justly be proud of.

Key Words: Asthma; airway inflammation; airway remodeling; infection; epithelial-mesenchymal trophic unit; ADAM33

INTRODUCTION

The word "asthma" originates from the Greek meaning *short of breath,* meaning that any patient with breathlessness was asthmatic. The term was refined in the latter part of the 19th Century with the publication of a treatise by Henry Hyde Salter entitled "On Asthma and its Treatment". In this scholarly work Salter defined asthma as "*Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks*", a description that captures his concept of a disease in which the airways narrow due to contraction of their smooth muscle.[1] His book contains remarkably accurate illustrations of the airways in asthma and bronchitis as well as the cellular appearance of asthmatic sputum some 30 years before Paul Ehrlich described aniline stains for eosinophils (eosin) and mast cells (toluidine blue).[2,3] He also described black coffee as a treatment for asthmatic spasms, a drink with a high content of theobromine, a derivative of theophylline and theophylline itself. This extraordinary insight into asthma stems from Dr Salter himself suffering from asthma himself. Thus, by the late nineteenth century, physicians adopted the view that asthma was a distinct disease which had a specific set of causes, clinical consequences, and requirements for treatment.

The father of modern medicine in the Western World, Sir William Osler (one of the three founders of the John Hopkins Medical School in Baltimore, US) described asthma in his first (1892) edition of the textbook Principles and Practice of Medicine[4] in the following terms:

1. Spasm of the bronchial muscles
2. Swelling of the bronchial mucous membrane
3. A special form of inflammation of the smaller bronchioles
4. Having many resemblances to hay fever
5. The affection running in families.
6. Often beginning in childhood and sometimes lasting into old age.
7. Bizarre and extraordinary variety of circumstances which at times induce a paroxysm:
    (a) Climate and atmosphere e.g. hay, dust, cat

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•There are no financial or other issues that might lead to conflict of interest.

(b) *Fright or violent emotion*
(c) *Diet (overloading of the stomach) or certain foods*
(d) *Cold infection*

8. Sputum is distinctive: rounded gelatinous masses ("*perles*") and Curschmann spirals & octahedral crystals of Leyden

These insights came as a consequence of Osler's drive to connect clinical observation with pathology and physiology. Asthma was treated largely a disease of "bronchospasm" since bronchodilators that included theophylline, ephedrine, adrenaline and by the first half of the 20th century, isoprenaline to be followed by the selective β_2-adrenoceptor agonists, salbutamol, terbutaline, remiterol and fenoterol by inhalation and as oral medications. However, their very effectiveness in reversing bronchospasm and their initial apparent safety led to their unrestricted use as over-the-counter medications. Over-reliance on bronchodilators was thought to underlie the epidemic of asthma death reported in Australia, the US and the UK that peaked in the mid 1960s (isoprenaline-related) and a second peak in New Zealand in the mid 1980s (high dose fenoterol-related).[5]

These asthma death epidemics drew into sharp focus the shortfalls in asthma treatment and emphasised how little was understood about why the airways of asthmatics were so liable to bronchospasm. Although since the early 1920s asthma death was known to be associated with extensive inflammation and structural changes in the airways,[6] very little was known about why this occurred and what relation it had to episodic bronchospasm. Indeed, asthma was largely managed as an acute disorder of episodic exacerbations. The discovery of *reagin* by Prausnitz and KÜstner in 1921 as a serum substance that could passively transfer allergy to a specific agent (in this case cod allergen)[7] subsequently led to the identification of IgE as the 5th immunoglobulin class IgE by Johansson and Ishizaka[8] and provided the crucial link. It turned out that most asthmatics exhibited allergy to a wide range of indoor and outdoor agents including dust mites, pollens and animal proteins.

THE BIRTH OF ASTHMA AS AN INFLAMMATORY DISORDER

Thus, by the 1980s a clearer understanding of how allergen exposure triggered chemical mediator release from airway mast cells (early reaction) and this resulted in turn led to the recruitment of eosinophils, basophils and mononuclear cells (late reaction),[9,10] the latter response being associated with enhanced airway reactivity to irritant stimuli (bronchial hyperresponsiveness – BHR). The allergic paradigm for asthma also explained why the mast cell stabilising agent, sodium cromoglicate, attenuated both the allergen-induced early and late bronchoconstrictor responses.[11] Clinical trials in the 1970s had also established that inhaled corticosteroids, notably beclomethasone di-

propionate – BDP, was a highly effective controller drug for asthma when taken daily.[12] The discovery that BDP reduced airway eosinophilic, mast cell and mononuclear cell inflammation[13] and abrogated the late asthmatic reaction and accompanying BHR with allergen challenge[14,15] created a mechanistic reason for their efficacy in controlling day-to-day asthma.

The mast cell had assumed centre stage as the principle triggering cell of asthma involving IgE-dependent activation with secretion of a wide array of autacoid, enzyme and proteoglycan mediators.[16] However, little was known about how mast cell activation-secretion coupling occurred. Changes in Ca^{++} flux was considered important as confirmed by the inhibitory effects of Ca^{++} channel blockers such as nifedipine. You Young Kim, while on a Research Fellowship in my laboratory in 1983, showed that the lack of stimulus-related specificity and the high drug concentrations required suggested that classical calcium channel blockade was not responsible for the inhibition of mast cell mediator release observed.[17] Although in the early 1980s histamine, prostaglandin D2, the cysteinyl leukotrienes [LTC4, LTD4 and LTE4 - previously known as slow reacting substance of anaphylaxis (SRS-A)], tryptase, chymase, heparin and exoglycosidases were all identified mast cell products with discrete proinflammatory effects, almost nothing was known about why mast cells were so sensitive to stimulation in asthma. At that time there was increasing interest in the role of T lymphocytes in underpinning the allergic response.[18] A large number of poorly characterised factors had been traced back to lymphocytes such as neutrophil chemotactic factor, eosinophil chemotactic factor, macrophage inhibitory and activation factors, the underlying connection between these and the allergic phenotype remained a mystery.[19]

THE IMMUNOLOGY OF ASTHMA

A breakthrough came with the identification of a special subset of T cells capable of secreting cytokines that selectively interacted with mast cells, basophils and eosinophils. These Th2-type T cells with their cytokine repertoire (IL-3, -4, -5, -9, -13 and GM-CSF) were responsible for the recruitment, priming and survival of the primary effecter cells of the allergic cascade.[20] In genetically susceptible individuals (atopic) allergens prevalent in the indoor and outdoor environment were detected by and subsequently modified by a third set of cells, the antigen-presenting population, especially dendritic cells (DCs) that accumulated at epithelial surfaces such as the airways. The last decade has witnessed a huge increase in knowledge about how DCs recognise allergens and communicate the specific sensitising signal to naive T cells involving Class II MHC restricted allergen peptide presentation to the T cell receptor (CD3) and engagement of co-stimulatory molecules.[21]

Thus, a combination of genetic susceptibility and allergen exposure is crucial to initiating and then perpetuating the allergic cascade via DC-T-cell communication. Because of genetic background and environmental exposures, asthma associated with allergens is likely to vary greatly. One particular subgroup which is particularly vulnerable is those exposed to allergens in the work-place.[22] Good example of this is the discovery by Kim et al that Citrus red mite (*Panonychus citri*) is the most common sensitizing allergen of asthma and rhinitis in citrus farmers in Korea.[23] Allergy tests, questionnaire and BHR measured in 181 citrus fruit farmers revealed a prevalence of asthma of 12.1%, rhinitis 17.1% associated with a positive skin-prick test to allergens from the citrus red mite of 16.5%, cockroach 11.0% and *Dermatophagoides farinae* 9.3%. Importantly, in farmers with asthma or rhinitis, allergy to citrus red mite was associated with to 54.5% and 68.5 % of subjects respectively thereby establishing a strong causal association in this exposed population.[24] Citrus red mite allergy also proved to be a common sensitizing allergen in children living around citrus orchards.[25] Another informative example of how local customs dictate allergic disease is the recognition of Korean ginseng-induced occupational asthma and the determination of IgE binding components.[26]

Beyond the recognition that allergen exposure in specific settings was a key step in the pathophysiology of asthma, the discovery that one could block the primary mast cell signalling cascade by directing a monoclonal antibody towards the IgE binding site to the high affinity receptor (FcεR1) without producing anaphylaxis was a great breakthrough[27] since this was the first specific biologic to be used in the treatment of severe allergic asthma.[28] Clinical trials of the monoclonal antibody, omalizumab, revealed efficacy as well as almost total inhibition of the early and late asthmatic responses to inhaled allergen.[29] Airway biopsy, blood and sputum studies also established the anti-inflammatory activities of omalizumab.[30] Cho et al. had established that pathological changes in the airways progressively increased according to the severity of asthma.[31] However, only one third to one half of patients with severe allergic asthma appeared to respond to omalizumab leading to the recommendation that treatment response at 16 weeks should be assessed using multiple endpoints. The reason why some patients with severe allergic asthma respond to omalizumab and others do not may relate to the extent that blockade of IgE binding to mast cells and dendritic cells produce down-regulation of FcεR1.[32]

THE ADDED COMPLICATION OF AIRWAY WALL REMODELLING

In addition to airway inflammation, there are extensive structural changes that occur in asthmatic airways that are especially prominent as the disease takes on a more severe and chronic phenotype.[31] These include epithelial mucous metaplasia, deposition of matrix proteoglycans and collagens in the submu-

cosa and between the bundles of smooth muscle, an increase in smooth muscle itself and proliferation of microvessels and nerves.[6] These changes are referred to as remodelling. The increased thickness of the subepithelial *lamina reticularis* is diagnostic of asthma and also increases with disease severity but not disease duration.[33] Indeed, this unique feature of asthma is present almost from the inception of the disease in early childhood[34,35] and, as in adult asthma, is associated with atopy since it is also present in atopic subjects with asymptomatic BHR.[36,37] It seems likely that such a response is the result of a dysfunctional airway epithelium which exhibits a breakdown in epithelial tight junction integrity compatible with impaired repair following injury.[38] This impairment of barrier function is also accompanied by increased expression of epidermal growth factor receptors (EGFRs) and accompanying tyrosine kinase phosphorylation and yet impaired epithelial repair.[39,40] This apparent conflict is explained by cell cycle inhibition resulting from increased nuclear translocation of the cell cycle inhibitor P21[waf] present at the inception of asthma.[34,41] However, as the disease becomes more severe and chonic, epithelial thickening and squamous metaplasia may occur.[33,42] EGFR activation is also a major pathway for epithelial mucous metaplasia and IL-8 production.[43] InterIeukin 8 (CXCL 8) and related chemokines (CXCL 1-7) are powerful chemoattractants by interacting with CXCR2 on the surface of neutrophils. Their increased production by a dysfunctional epithelium[44] may explain the increased neutrophil prominence observed in more severe and corticosteroid refractory asthma[45] as well as in the airways of asthmatic patients who smoke.[46]

Impaired wound healing and failure to form adequate tight junction assemblies are phenotypes that persist when asthmatic epithelial cells are cultured *in vitro* and differentiated at an air liquid interface suggesting that the epithelium is primarily defective in asthma.[38,47] In this respect, it is of interest that many of the newly identified genes that increase asthma susceptibility are preferentially expressed in the epithelium (e.g. *DPP10, SPINK5, GPR 154, HLA-G, MUC8,* chitinase 3-like-1 (YKL-40), *PCDH-1*, ORMDL3 and GSDLG).[48] Altered barrier function has also recently been recognised as an important feature of atopic dermatitis (filaggrin mutations),[49] food allergy[50] and rhinosinusitis.[51] In addition to innate defects in barrier function, environmental agents such as biologically active allergens (dust mites, pollens, fungi and occupational allergens e.g. proteases in washing powders) and virus infections are potent agents that can attack tight junctions.[52,53]

In addition to alterations in physical barrier function, the airway epithelium in asthma my also be functionally deficient. One example of this is the reduced ability of the airway epithelium to protect itself against oxidant injury both directly (tobacco smoke and outdoor air pollutants – ozone, oxides of nitrogen and particles),[54] all known to drive deterioration in asthma control. A further example is the ease with which common and usu-

ally innocuous respiratory viruses (e.g. those that cause common colds) can cause serious deterioration in asthma control (exacerbations) leading to the necessity to increase treatment, seek medical help or require hospital admission.[55] Yearly monitoring of asthma in the Northern hemisphere reveals a cyclical nature to exacerbations both in the community and in hospital admissions.[56] A large September-winter peak is followed by smaller spring and summer peaks. The former is driven by virus infection involving a wide variety of viruses but dominated by the subclasses of rhinovirus, while the latter smaller peaks relate more peaks of pollen exposure (e.g. tree followed by grass). The recent discovery of a new clade of rhinoviruses (Type C) seems to be especially linked to asthma exacerbations.[57] In more tropical climates the seasonality of asthma exacerbations is no longer apparent, suggesting that climatic conditions are important for creating this periodicity.

ASTHMA EXACERBATIONS, THE ROLE OF INFECTION

An important question that requires answering is why the asthmatic airway is so vulnerable to respiratory virus infection. Using epithelial cells cultured in vitro, it has been shown that those from asthmatic subjects are more resistant to apoptosis induced by rhinoviruses leading to increased virus replication followed by cytotoxic death of the cell with enhanced virus shedding.[58,59] Both for the major and minor rhinovirus subtypes, this defect in viral defence is a direct consequence of impaired production of the primary interferons (IFNs) IFN-β and λ. These cytokines represent the first line of defence against respiratory viruses through their double strand RNA interacting with endosomal toll like receptor (TLR) 3 to phosphorylate the transcription factor Interferon Regulatory Factor (IRF) 3 that on binding to the interferon sensitive response element in nuclear DNA leads to the induction of IFN α and β (the primary anti-viral response) that in turn activate the common interferon receptor to phosphorylate STAT1 that interacts with IRF and gamma-activated sequence (GAS) to induce the production of a wide range of antiviral proteins such as Mx1, IFI1, IFI204, IRF7 and IP10 (secondary anti-viral response).[60] This abnormality in innate immunity provides a unique opportunity for treating severe acute exacerbations with inhaled human IFN-β which is now in clinical trial.

The discovery that both barrier function and innate immunity in asthma are abnormal reinforces the pivotal position that the airway epithelium is in to orchestrate cellular events of asthma. A recent important development is the observation that rhinovirus infection in the first 2 years of life is a much more powerful risk factor than allergen exposure at this age.[61,62] Indeed it is now looking increasingly likely that impaired epithelial functions predispose the genetically at risk child to developing asthma involving a wide array of environmental insults such as common respiratory virus infections, air pollution, exposure to

irritant chemicals (e.g. tobacco smoke) with these factors enhancing the ability of airway dendritic cells (DCs) to overrespond or respond differently to environmental allergens.[22] Since Rate and colleagues have recently shown that epithelial production of IFN-β is the principle factor in driving airway DCs down a Th1 pathway, reduced production of this primary interferon may account as occurs in asthma may account for the biased Th2 response that occurs in this disease.[63] A deficiency in recruitment of plasmacytoid DCs may further exacerbate virus-induced wheezing in those destined to develop asthma in childhood.[64] Additional factors include the enhanced production of Th2 polarising cytokines such as thymic stromal lymphopoietin (TSLP),[65] IL-35 (a newly identified member of the IL-1 family),[66] CCL5, CCL17 and CCL22.[67]

THE EMTU, REMODELLING AND ADAM33

Susceptibility to asthma may also reside in the matrix and smooth muscle components of the airways. In 2000 we suggested that in asthma reactivation of the epithelial-mesenchymal trophic unit (EMTU) that is normally involved in foetal branching morphogenesis, leads to exuberant release of a range of growth factors that drive the increase in smooth muscle, angiogenesis and deposition of matrix[68] that drive the initial modelling and then remodelling of the entire airway wall in proportion to the disease subphenotype. Such a model embraces the wide number of environmental insults such as associated with asthma at its onset, during exacerbations and in its progression.[69] One susceptibility gene associated with the EMTU is ADAM33, the first novel asthma gene to be positionally cloned. ADAM33 is encoded on chromosome 20p13 and is tightly regulated in its expression, being limited to mesenchymal cells such as smooth muscle and fibroblasts.[70] Although consisting as 21 exons encoding multiple functions, the metalloprotease activity has aroused most interest as it is potentially "druggable". Polymorphic variation of ADAM33 has been associated with childhood onset asthma and BHR, impaired lung function in infancy, accelerated decline in lung function that occurs in severe asthma and most recently, COPD.[71] In a landmark publication, Lee and colleagues discovered that rather than existing solely as a membrane-associated protein of 120kD, ADAM33 can be cleaved into a soluble fragment of 55kD.[72] sADAM 33 expressing the catalytic subunit immune-localises to the asthmatic epithelium and to the *lamina reticularis* beneath the basement membrane as well as to mesenchymal cells. In asthma airway levels of sADAM33 increase in proportion to disease severity and inversely with lung function. Using the soluble catalytic subunit, we have recently shown that ADAM33 is a powerful angiogenesis factor[73] as well as increasing smooth muscle in developing foetal lung. Thus, although being identified as an asthma gene, it is looking increasingly as if ADAM33 is a gene involved in multiple aspects of airway modelling and remodel-

ling.

PROFESSOR YOU YOUNG KIM: A TRIBUTE

In concluding this brief review, I wanted to say a few words about Professor You Young Kim. Professor Kim first joined my research group in Southampton, UK in 1983 when, as mentioned earlier, he studied activation-secretion coupling in human mast cells and basophils with Martin Church and me. Professor Kim was my first overseas Research Fellow (Figure) and blazed a trail that others were to follow. On his return to Seoul in 1984, he set about building Allergy as a clinical and scientific speciality in Korea. His achievements are little short of outstanding. His enthusiasm to embrace the full spectrum of clinical and scientific aspects of allergy from the most basic to the most applied, his championship of encouraging only the very best level of clinical service and scientific endeavour and his strong belief in encouraging the younger generation to strive towards excellence is truly admirable. Over a span of 25 years he has propelled Korea into the forefront of the field of allergy that is truly in the top league internationally. This has been recognised by the high quality congresses that he and his colleagues have organised in and brought to Korea. It is therefore a fitting tribute of his esteem that the 2015 World Allergy Congress will be held in Seoul Korea. I and my colleagues in the UK wish Professor You Young Kim a very happy and well deserved retirement from his University post. He leaves with the clear knowledge that all his labours have translated into outstanding success. I am sure Sir William Osler, if he was still alive, would be as proud as I am to have been associated with this extraordinary man and his achievements.

Figure. Prof. You Young Kim (right) and the author. This photograph was taken during Prof. Kim's overseas Research Fellowship at Southampton University, UK in 1983.

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