WHY IS ASTHMA ON THE INCREASE: NURTURE VIA NATURE

ANURAG AGRAWAL* AND BALARAM GHOSH

Interplay of genes and environment determines health. While we are born with our genetic constitution defining our inherent nature, its phenotypic expression is heavily dependent on the continuum of environment during nurture. In this context, we look at the recent global increase in asthma prevalence, and find that changing dietary habits, lifestyle and other environmental factors such as air pollution may induce asthma in genetically susceptible individuals through complex metabolic disturbances. Allergy may be an outcome, not necessarily the cause, of such changes. Thus the question in asthma is no longer whether it is the genes (nature) or environment (nurture), but how the changing nurture is influencing a natural propensity. Some answers have been found and more are needed.

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Institute of Genomics and Integrative Biology, Council of Scientific and Industrial Research -(CSIR), Mall Road, Delhi-110007, India.

* Corresponding author Anurag Agrawal (a.agrawal@igib.in)
Phone 91-11-27666156, Fax 91-11-27667471.

Asthma is a disease characterized by spontaneous but reversible constriction of the airways which results in breathing difficulties1,2. Commonly asthma is associated with allergies and triggered by seasonal or perennial allergens such as pollen or house dust respectively. This is often associated with cough and wheezing and asthma is often referred to as “wheezy bronchitis” or “allergic bronchitis”. In other cases asthma may be more surreptitious, occurring with identifiable triggers such as exercise, aspirin like drugs, or can sometimes occur unpredictably as well. There has been a steady rise in the prevalence of asthma locally, nationally and globally. To ascribe this increase solely to increasing air pollutants is naïve since the highest rates of asthma are seen in western countries (as high as 30%) where air quality, as judged by common pollutants, is much better than in Indian metropolitan cities like Delhi (about 10%).

A more recent hypothesis, termed the hygiene hypothesis, sought to explain this anomaly as being an outcome of relatively immature immune systems, which had been insufficiently stimulated because of increasing hygiene. This would explain why countries like India and China, with worse air quality than many western countries, had lower levels of allergic diseases and asthma. Yet this hypothesis too falters in the face of emerging epidemiological data that shows children coming from low socioeconomic strata of urban America to be at higher risk of asthma than their affluent counterparts. Very interestingly, the reverse has been noted in India with more affluent school-children being at higher risk of asthma. This has led to emerging concepts of lifestyle related asthma where consumption of calorie-rich and nutrition-poor food products (junk foods) is a risk factor for development of asthma, along with other factors as described above, in those who are genetically predisposed towards it. This is supported by strong epidemiological evidence from dozens of studies that relates obesity to increased asthma risk3. While other factors such as air-quality, smoking, exposure to bacterial endotoxins and et cetera are also important players, and a family history of asthma remains the most important single factor, this concept most successfully explains the sudden recent rise in asthma over the last decade. Increased life-expectancy in the face of increased morbidity and health-care utilization makes this an expensive public health problem that begs attention. In addition, recent evidence of increasing incidence of steroid resistance in asthmatics has aggravated the situation further. Therefore identifying and modifying the specific factors that predispose individuals towards asthma is important.
It can be seen from common experience and has been proved scientifically in twin studies, that asthma has a strong heritable component, often being seen running through families. This inherited tendency to asthma approximately accounts for about half of the asthma risk with lifestyle and environment presumably contributing the rest. Thus a good approach to start understanding the fundamental processes causing asthma is to define the shared genetic traits between asthmatics and relate them to environmental and lifestyle related factors that together cause asthma. From a genetic standpoint, asthma is a complex disorder, meaning that no single gene or other factor can provide a simple explanation; combinations of many interacting genetic variations, further influenced by environmental factors (including lifestyle), being the most likely model. Our laboratory has been extensively involved in such research and the remainder of this article will discuss some of the insights into asthma that we have gained over the years.

There are two basic ways to discover genetic risk factors and both of these are used in asthma studies. In the first approach, genetic profile of people at high risk for disease can be contrasted with that of people at low risk. In practical terms, subjects with disease (cases) are used to approximate people at high risk and similarly matched aged subjects (from the same ethnicity and geographical location) without disease (controls) are used to approximate people at low risk. In the other approach, the occurrence of disease is investigated in families, looking for those genetic variants that associate with disease. We have used both types of studies to try to understand the immunological and metabolic basis of asthma. It is well known that asthma, particularly of the allergic type, is related to a type of immune response referred to as Th2 response. Th2 refers to T helper cell type 2, which promote an immune response dominated by secretion of cytokines like interleukins-4 and 13, immunoglobulin (Ig)-E production by B cells, eosinophil and mast cell influx and activation. We have identified a number of variations in the genes that direct the Th2 response or its counterbalance, the Th1 response (T helper cell type 1, characterized by interferon-gamma), that are associated with asthma. Importantly, we see that variations between the Th1/Th2 genes interact with each other to confer greater risk than individual variations do by themselves. A large number of genes seem to be involved including cytokines such as interleukins 4, 10, 13; cytokine receptors such as interferon gamma receptor; receptors to IgE antibodies et cetera. Based on a number of publications from around the world, currently almost a hundred genes are thought to be associated with asthma risk. While a majority of them have been linked to inflammatory processes, partly because of biases in selecting genetic candidates, recent studies that examine the entire genome in an unbiased manner (genome-wide association studies) point strongly toward novel pathways related to lung structure and function. In our own lab, using a relatively unbiased approach (linkage), we found a polymorphism in inositol phosphate 4-phosphatase A (INPP4A) gene to be associated with asthma risk in Indians. This was a novel discovery at the time and has been replicated by others since. Interestingly, in a separate unbiased study using genome-wide transcriptional profiles of cells from lungs of asthmatics and normals, we found independent evidence of abnormalities in inositol signaling pathways in asthma. This is particularly interesting because these are fundamental signaling pathways closely linked to cellular metabolism and are known to be altered in other disease states like obesity related metabolic syndrome, hypertension, diabetes, and cardiovascular disease. These, particularly hypertension and metabolic syndrome are strongly associated with asthma risk in large population studies, but the mechanism has so far been unclear.

Ongoing work in our laboratory is projected to confirm these associations and define the mechanisms in experimental models of asthma. Asthma is a disease specific to humans, with the exception of asthma like symptoms naturally occurring in some horses (heaves) and airway hyperresponsiveness naturally seen in basenji greyhounds. However features or processes of asthma can be modeled in a variety of animals like guinea pigs, mice, rats, sheep, dogs, and non-human primates. For reasons mostly related to convenience, rodent models, particularly mouse models, are most commonly used. Typically, a mouse is made allergic to a foreign protein like ovalbumin (egg white) by injection along with adjuvants like alum. After an allergic response is established, inhaled aerosols of the allergen i.e. ovalbumin are administered to cause allergic inflammation of the lungs. This leads to the development of airway hyperresponsiveness and structural changes such as development of mucus secreting cells (goblet cells). Such models have been extensively used to characterize the immune aspects of allergic asthma and the remodeling of the airways. Most of the genes found to be important in asthma by others and by us have now been validated in mouse models. Importantly, it has been shown that a number of environmental triggers such as diesel exhaust particles, cigarette smoke, fungal allergens can predispose to development of asthma in such models or aggravate it if already established. Interestingly, similar to human observations, stress and/or obesity can lead to increased
asthmatic risk in mice. These facts have led our laboratory to consider that there may be important metabolic changes occurring in the lung during development of asthma and universal strategies to combat asthma may emerge from arresting these processes rather than focusing exclusively on allergy. An important metabolic change that is well known in human asthma is that Nitric Oxide (NO) gas content of exhaled breath is increased. The source of this gas is considered to be the airway epithelium. NO is synthesized through catalytic breakdown of L-arginine, an amino-acid, by constitutive and inducible Nitric Oxide Synthases (eNOS and iNOS respectively). While eNOS, also referred to as eNOS, produces small quantities of NO in a calcium dependent regulated fashion; iNOS is in a stably activated state and produces large quantities of NO. Using a novel method of measuring exhaled NO, devised in our lab, we verified that mice with experimental asthma also have increased exhaled NO. Further, we found that the increased exhaled NO is due to increased iNOS in airway epithelial cells and inflammatory cells, with reduced levels and function of eNOS in airway epithelial cells. A methyl derivative of arginine (asymmetric dimethyl arginine [ADMA]) is known to inhibit eNOS by competing with L-arginine in binding to the catalytic site but not being catalyzed further. This leads to generation of reactive oxygen species which when combined with NO from iNOS form reactive nitrogen species. The entire process is well understood in obesity related cardiometabolic syndrome where high levels of circulating ADMA prevent endothelial cells of blood vessels from synthesizing NO, leading to inadequate dilation of blood vessels, and thereby hypertension. The increased oxidative stress and altered lipid metabolism additionally leads to atherosclerosis, and current therapies include use of “statin” drugs that inhibit ADMA production along with their well known effects in reducing cholesterol synthesis. We found that ADMA is also increased in lungs of asthmatic mice, so much so that asthma was sufficient to increase circulating ADMA as well. This increase was due to increase in methylation enzymes (protein methyl transferases) and reduction in the ADMA degradation enzymes. Strategies to counteract the effects of ADMA, such as supplementation of L-arginine or use of statin drugs, were effective in reducing asthmatic features in mice. This is interesting because the mice remain allergic, receive allergen exposure to the lungs, yet the development of features of asthma is inhibited by purely metabolic strategies. In the case of L-arginine, it has been found that dietary supplementation may be useful in treating metabolic diseases such as hypertension; it now seems that it may be helpful in preventing or treating asthma as well. However, further human research is needed before any firm conclusions can be reached. Other possible strategies include use of statins. A hypothesis that has been put forward recently is that junk foods are low in natural antioxidants while consumption of fresh fruits, vegetables provides a rich variety of antioxidants. Thus a junk food diet, in addition to promoting obesity, may directly predispose to oxidative damage of the lungs, which are exposed to many environmental pollutants. Thus an urban unhealthy lifestyle may predispose to asthma, as is being seen today. Protective strategies may include supplementation with antioxidants, which we have found effective in mouse models, or bolstering the body’s own antioxidant response. The latter is governed by a master regulator protein Nrf2, elegantly described by Dr. Shyam Biswal at Johns Hopkins University, to be a critical determinant of lung pathology during environmental stress conditions. It has been shown that certain dietary components can promote nrf2 mediated antioxidant defense, and this may form the basis of novel therapies in the future.

Slowly the focus of research in asthma has shifted from immune response to the lung, with the epithelial and mesenchymal cell responses and interactions becoming particularly important. It is now conjectured that rather than allergy coming first and causing damage to the lung, it may be an abnormality of the lung that predisposes to allergic response to inhaled allergens. This can clearly be seen at the genetic level where genes such as Dipeptidyl peptidase (DPP) 10 and disintegrin and metalloproteinase (ADAM) 33 expressed in the epithelium and mesenchyme respectively, have emerged as major modulators of genetic risk of asthma. At a functional level, sub-cellular dysfunction of organelles such as mitochondrion and endoplasmic reticulum of airway epithelial cells may also contribute to asthma pathogenesis. In mice, it is shown that mitochondrial dysfunction in epithelial cells is associated with asthma and pre-existing dysfunction may enhance development of allergy. Failure of cellular calcium homeostasis, partly related to failure of smooth endoplasmic reticulum associated calcium pumps, and partly to complex rearrangements of sodium-calcium homeostasis, has been implicated in excessive airway smooth muscle contraction. Notably, Dr. Krishna Agrawal at Vallabhbhai Patel Chest Institute, India, in collaboration with colleagues at Centre of Biochemical Technology (now IGIB), proposed two decades ago that asthma is not simply allergy driven, unlike allergic rhinitis, but represents a complex metabolic disturbance. Today the wheel has come full circle.

In summary, each of us is born with a set of genetic variations compared to an idealized normal that defines a
risk profile for health and disease inherent to our nature. Specifically for asthma, these may represent a propensity towards a Th2 response, an attenuated Th1 response, a tendency towards increased inositol signaling et cetera. These are complex not only in that multiple genes are involved but also that this influences many other aspects of health and cellular function, beyond a singular disease. For example a powerful Th2 response can protect against intestinal parasites, common in India. External factors such as allergens, air pollution, diet, exercise, stress, smoking et cetera, then potentiate the system further. Mal-adaptation to these stresses results in disease, with likelihood varying amongst individuals based on their genetic nature and perhaps sheer chance. The recent explosion in asthma incidence cannot be due to a change in the genetic nature, being relatively fixed, but because of rapidly changing lifestyles in a genetically predisposed population. Thus the question in asthma is no longer whether it is the genes (nature) or environment (nurture) but how the changing nurture is influencing a natural propensity. Some answers have been found, and more are needed.

References