Departement Biomedizin Basel

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Pneumology & Pulmonary Cell Research

The genetic and epigenetic nature of susceptibility to chronic inflammatory lung diseases

The prevalence of asthma and chronic obstructive pulmonary disease (COPD) are increasing worldwide and represent a major issue for daily life for all patients. According to the World Health Organization, 280 million people suffer from asthma and up to 40% of children suffer from asthma symptoms. In 2015, 65 million people were diagnosed with severe COPD with a death rate of 3 million/year. Both diseases are characterized by (i) chronic airway inflammation which can be controlled by pharmaceutical drugs and (ii) airway wall remodeling which is insensitive to drug therapy. The American Thoracic Society stated in 2016 that chronic inflammatory disease may not be cured unless we understand the cause of airway wall remodeling.

Gene linkage analyses suggested that the susceptibility to develop asthma or COPD can be inherited, but despite the identification of 182 candidate genes, none of them had been proven as a cause. Family studies showed heritability; while twin studies indicated that genetic conditions contribute less than 50% likelihood to develop asthma. Recent studies investigated the regulation of gene regulatory factors and suggest that these epi-genetic mechanisms may present as inheritable pre-condition to develop asthma or COPD. Other studies provided evidence that the lung needs to be prepared (imprinted) during embryogenesis and early childhood to develop asthma or COPD later in life. The nature of this imprinting process seems to be due to epi-genetic events, but is not well understood.

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Several epi-genetic mechanisms have been investigated in the context of imprinting the lung for asthma or COPD, including chemical modifications of histones and DNA. These events will lead to over-expression of inflammatory proteins or shut-down of anti-inflammatory proteins. Other epi-genetic events can occur through modified microRNA regulation or RNA stability regulating proteins, which are often associated to mitochondria activity. Importantly, the activation of the named epi-genetic mechanisms can occur through the exposure to asthma or COPD risk factors such as inhaled allergens, chemicals, cigarette smoke, and dust, as well as by physical and psychologic stress factors.

A major problem for the studies of epi-genetic mechanisms as a pre-determining factor for asthma and COPD is the fact that most animal models for both diseases are not reflecting the human disease fully. In order to understand the pathologic events and to find new therapies, investigators need access to data and tissue banks generated from human asthma and COPD lungs.

Models which are based on large data collections from the USA, Europe and Asia showed that outdoor air pollution caused 3.3 million premature deaths worldwide in 2015, and this number is expected to double by 2050. Further 3.5 million people died from indoor pollution caused by open fire cooking and heating. Air pollution does not only originate from industry and traffic; it is also caused by fine dust (<10 pm) form agriculture in less industrialized countries. A survey by the European Union in 2016 stated that in Europe 50% of chronic inflammatory diseases are misdiagnosed and inadequately treated.

Over the past 20 years genetic studies in asthma and COPD linked 182 genes to the inheritance of asthma and COPD. However, none of these candidate genes had ever been proven to be a single cause of the diseases. There is evidence that modification of gene regulation during embryogenesis imprints the lung to develop asthma or COPD later in life. Family studies were performed over three generations suggested that, the imprinting of the lung by cigarette smoking and COPD could be traced back to grandmothers and may have skipped one generation.

Studies in rhesus monkey showed that several asthma pathologies were induced by exposure to allergens, cigarette smoke, or increased oxygen radicals during pregnancy and early infancy. In rhesus monkeys and humans, the susceptibility to develop asthma was associated with the exposure of mother and child to the same risk factors during late embryogenesis (last trimester) and early childhood (0-6 years) respectively. Low levels of zinc ions in mother and child during pregnancy correlated with an increased risk of asthma in children. Zinc is an important regulator of zinc finger proteins which regulate hormone-dependent gene activity, RNA transcription and protein synthesis, which all can be regarded as epi-genetic

regulators. Malnutrition during pregnancy increased the risk for the child to develop asthma, wheeze, and atopic diseases later in life. In addition, risk factors for asthma can be transmitted from mother to child by breast feeding. There is also evidence for multi-generation transmission of asthma susceptibility, as mothers exposed to phthalates during pregnancy increased the risk for the next two generations to develop asthma. The exact mechanism of this trans-generational asthma susceptibility is unknown, but experimental and clinical data suggested that it is due to DNA and histone methylation and modified microRNA expression.

DNA methylation was studied in 527 children (aged 5-12 years) who were born to cigarette smoking mothers and identified 20,578 methylated DNA sequences. Most of the genes were methylated at stretches of CpG repeats with unknown function. In a second study with a cohort of 572 children, DNA methylation caused by cigarette smoke was linked to respiratory symptoms at the age of 3-5 years. Tobacco smoke induced gene specific methylation of at least 10 folds in 26 different genes, including the aryl hydrocarbon receptor repressor (AHRR) and cytochrome P450 (CYP). Both proteins are known to be deregulated in other diseases caused by cigarette smoking. However, 50% of the affected genes encode for unknown proteins or microRNAs. In another study consisting of 245 females, aged 10 - 18 years, DNA methylation analysis affected mainly genes encoding for Th2 cytokines, which are known to be increased during asthma. It has to be investigated if these DNA methylation patterns in children exposed to risk factors are identical to those described in adult asthma.

In rhesus monkeys, the exposure to allergens during pregnancy and of the new-born directly after birth resulted in lasting asthma pathologies including disturbed interaction of epithelial cells with smooth muscle cell, as well as in smooth muscle hypertrophy, cytokine expression, and vascular remodeling of the airway wall. Importantly, none of these pathologies was repaired later in life. This data indicates that a once damaged lung stays damaged and

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cannot regain the structure of a healthy lung. The molecular mechanisms (transcription, translation, methylation, etc.) by which allergens cause constitutive activation of pro-inflammatory signaling pathways is unclear.

The inheritance of epi-genetic events would be most effective if they occur in mitochondria genes, which are only forwarded to the next generation by the mother. Malfunction of mitochondria was reported in human asthma and correlated with airway smooth muscle cell hyperplasia and increase secretion of pro-inflammatory cytokines. Epigenetic deregulation of mitochondria genes was associated with aging, resetting gene regulation during embryogenesis, inflammation, proliferation, and cell differentiation. However, the cause of the increased mitochondria mass was not explained.

MicroRNAs represent a novel level of epi-genetic regulation, and function as regulators of RNA-protein translation, RNA stability and mitochondria activity. Regarding asthma and COPD, 27 different microRNAs have been linked to organ malfunction and disrupted cell-cell interaction. However, most details of these mechanisms are yet to be investigated.

In summary, two time windows during late embryogenesis and early childhood determine the maturation, function and structure of the lung for the rest of the life. The susceptibility to develop asthma and COPD may not be inherited through a genetic pre-condition, but rather by irreversible epigenetic events. Future studies need to investigate how epi-genetic modifications become "fixed" and inheritable. Mothers have to become better informed about these risk factors and that they can do more to prevent their children from suffering lifelong lung malfunction. Finally, the interaction of basic, clinical and epidemiological research is needed for better understanding the cause of asthma and COPD in order to find new therapies.

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Asthma: How to treat and prevent the high impact disease

Sereina de Zordo from the aha! Swiss Allergy Centre outlines the global burden of asthma and how through various methods and programmes it can be managed

Wheezing, chest tightness, shortness of breath and cough – these are typical symptoms of allergic asthma. It is characterised by a chronic airway inflammation and spasmodic narrowing of the airways. Symptom frequency, intensity and their impact on quality of life vary individually. Asthma is a potentially serious and sometimes fatal chronic disease[1].

A global burden

Furthermore, asthma is a major health problem, affecting around 300 million people worldwide and causing annual costs of €17.7 billion in Europe. In Switzerland, around 12% of children and 6% of the adult population are suffering from the disease.

Allergies mainly against indoor and outdoor allergens originating from pollens, house dust mites, domestic animals or moulds, as well as occupational allergens are the most common causes of allergic asthma. Viral infections, dust, odours, smoke, pollutants or exercise are factors which enhance or trigger the asthma symptoms. Untreated or poorly treated allergic rhinitis (e.g. caused by pollen allergy) leads to asthma in around 30% of the allergic patients. Consequently, with proper diagnosis and treatment of allergies and asthma, €142 billion could be saved per year in Europe. An appropriate diagnosis by specialists apparently is of fundamental importance[2, 3].

Asthma-management

The ultimate goal of an adequate asthma therapy are no exacerbations, no restrictions in everyday life, no nocturnal awakenings, optimum lung function and any necessary emergency treatments.

First and foremost, contact with the allergen has to be avoided or reduced as much as possible. Therefore the first imperative is to identify the allergens and triggers and, if possible, to eliminate them in order to prevent asthma attacks.

Medical treatment to reduce symptoms may include individually tailored medicines, which dilate the airways and e.g. steroids for a long-term treatment to ease swelling and inflammation.

After thorough investigation, specific immunotherapy is often recommended for allergic asthma. This is a causal treatment by increasing the tolerance to a specific allergen and no longer triggering an allergic reaction. For this subcutaneous or sublingual treatment, a well-controlled or rather intermittent or mildly persistent asthma is required, dependent on the eliciting allergen. On an economic level, the cost-effectiveness of immunotherapies in allergic asthma patients overweighs the pharmacotherapies on a long-term basis[4].

The need for educational programmes and prevention

Effective asthma-management has to be completed by additional education on a patient's level. Structured patient's education programmes lead to improved clinically relevant conditions, better self-management and symptom control, as well as higher life quality. Combined with exercises for symptom recognition, adaptations in therapy and emergency treatments as well as in the inhalation techniques are essential[5]. Recent Swiss studies show that 6 out of 10 asthma patients do not use their inhalation devices correctly and that there is a need for educational programmes[6].

In Switzerland, aha! Swiss Allergy Centre together with the Lung Association are leading project partners by offering such patient's asthma courses.

There is a worrying increase in asthma and allergy prevalence almost worldwide. To take into account not only the economic costs but also, in particular, the burden of the disease in all affected people, the consideration of prevention factors related to atopic diseases is crucial. Based on the German guidelines on allergy prevention, there is data for different preventive factors against the development of asthma. Regarding allergy prevention, the following exposures should be avoided: active and passive tobacco smoke exposure, obesity, indoor air pollution and outdoor air pollution like nitrogen oxides or particulate matter (e.g. PM2.5 or PM10)[7].

There is further need for information in the population regarding allergy and asthma prevention. An appropriate diagnosis, as well as an effective short and long-term treatment, is also a crucial factor. This is where patients, doctors, as well as health organisations should closely work together – to treat and prevent the high impact disease.

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4 Pfaar et al. Guideline on allergen-specific immunotherapy in IgE- mediated allergic diseases – S2k Guideline. Allergo J Int 2014;23:282–319.

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6 Dürr et al. J Asthma. 2016 Nov;53 (9):955-63.

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