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THE DEVELOPMENT STAGES OF IMMUNE SYSTEM. ROLE OF GENE-ENVIRONMENT INTERACTION IN THE ALLERGIC DISEASE MANIFESTATION.

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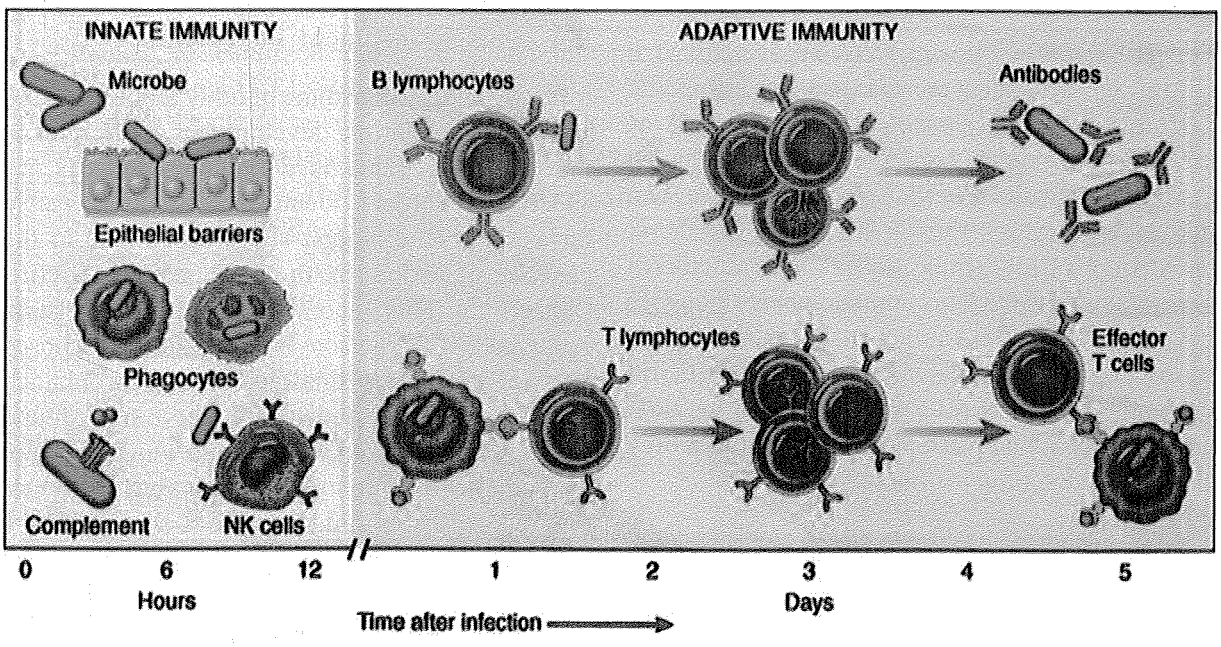
Abstract:

The increasing prevalence of the allergic disease is urging a solution. Many studies have demostrated that the predisposition to develop allergic disease is strongly related to the model of the immune system development. The clear clue until now is the Th 2 response in allergic individuals. This deviation begins in utero and continues in early life under environmental exposure including nutrition, microbiome, activity patterns, and modern pollutants. In this way, understanding the common risk factors responsible for one disease means to find the common solutions to prevent them.

The Immune system and the differences between atopic and non-atopic children

The immune system is a well-organized network composed of lymphoid organs, cells, and cytokines. The main function of this system is the host defence. His role can be better shown in cases of **underactivity**, resulting in severe infections and tumours, or **overactivity** being responsible for allergic and autoimmune disease. Immunity is divided into two parts which are different in their speed and specificity of action. The first one is the **innate immunity** which includes the physical, chemical, and microbiological barriers also neutrophils, monocytes, macrophages, complement, cytokines, and acute phase proteins. It acts immediately and not specifically. The second is the **adaptive immunity** which consists of antigen-specific reactions mediated by T and B lymphocytes. It is characterized by delayed and specific mode of action (1).

Fig.1 Immune system



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Both systems are immature at birth. The maturation continues in the postnatal period under the exposure to different environmental stimuli changing in this way the gene expressions. These agents are named epigenetics factors. Epigenetic studies the changes of gene activity which are inherited and are not caused by changes in DNA sequence but from histone modifications (methylation and acetylation) and DNA methylation. Both the genetic predispositions and the epigenetics factors contribute to the risk of developing asthma and other allergic disease (2). The prevalence of allergic disease is increasing worldwide so it is becoming more and more necessary to find the causes in order to intervene and prevent them (3). In patients with allergic disease the distinguishing feature of the immune response, seen at any age, is the Th 2 type,(4) but in some studies (5) is shown that the Th 1 cytokine production in atopic children is not necessarily deficient compared with the nonatopic. There is evidence supporting that events and exposures during pregnancy and early life may deviate the immunological response toward one pattern or the other (6,7). In a longitudinal cohort study was examined the effects of postnatal microbial exposure on T-cell ontogeny in 739 infants followed from birth and at 1, 2.5, and 5 years of age. This study demonstrated two different types of maturation of the immune system in allergic and non allergic children. In the non-allergic children the innate immune system is immature at birth with age-related maturation that continues for a long time and correlates with an increase in the Th1 response to allergens and mitogens. In the allergic children in the perinatal period there is a higher inflammatory response with a relative decline in the postnatal maturion.

The Th1 function remains weak but is associated with an age-dependent increase in allergen-specific Th2 response (8). These different patterns of immunity development observed at birth emphasize the important role of *in utero* factors. Also is seen that having an atopic mother is a greater risk factor than an atopic father suggesting an uterin programming of the fetus immune system that goes beyond genetics (9). Another cross-sectional study trying to give the explanation of the variability in the immune system (10) was conducted by *Tulic* using samples taken from the thymus of healthy children undergoing cardiac surgery.

The conclusion achieved was that in atopic children Treg cell maturation was significantly delayed compared with that seen in age-matched nonatopic children.

Evolution of the "hygene hypothesis"

In 1989 David Strachan formulated the well-known "hygiene hypothesis", (11) which in summary, stated that atopy could be prevented by infections in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally. According to this theory, the "natural immunity" to bacterial and viral infections induces the production of cytokine by Th1 lymphocytes, attenuating the Th2 immune response which is involved in the allergic disease. But the results of the studies which have directly addressed infection as the responsible factor have not been able to support this mechanism and sometimes were difficult to be interpreted (12). Lately researches are concenrtated in the influence of intestinal bowel flora or microbioma on immunological maturation, and also the modulating effects of antibiotic therapy, shift in nutriens, and acting through gut flora. Microbiome is the set of microorganisms, their genetic material (genome) and their interaction with the surrounding environment in a distinct location i.e.: human body. Many authors differentiate the term "microbiome" from "microbiota" to describe respectively, the set of microorganism's genome for the first and the microorganisms themselves for the second one. Given that it is not yet established a direct link between infections and allergic disease, the "hygiene hypothesis" is being adapted in the "microbiota hypothesis" (13) meaning that changes in microbiome due to different stimuli deviate the maturation of the immune system toward one pattern increasing the possibility to develop allergic disease. Thereby the human microbiome represents a key environmental trigger in people with genetic predisposition (9).

The gene-environment interaction

A family history of asthma or other atopic diseases is a risk factor for the development of allergies in the offspring. This is why many studies are undertaken in order to identify the genes responsible for asthma. The largest study up to date in the genetics of asthma is the European GABRIEL Consortium. This genome-wide association study genotyped 10,365 persons with physician-diagnosed asthma, and 16,110 unaffected persons obtained from 23 individual studies (14).These study found different genes linked with asthma which were not the same for different age groups, but the genes found for asthma did not give a signal for the production of Ig E antibodies. In this way, where we don't have the responsible gene nor the responsible environmental trigger, the manifestation

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of the allergic disease happens when there is the right combination between the genetically predisposed individual exposed to environmental triggers. There are a number of possible gene-environment interactions where the environment has an effect in subjects with a certain genotype, or in others, the socalled cross-over interactions, where genotype and exposure have effects, but the interaction is in opposite directions (15).

Conclusion

Asthma is a multigenetic and multifactorial disease in which the genetic predisposition combined with environmental exposure lead to the manifestation of the disease. The predisposition to develop allergic disease begins in utero and goes on in early life. This conclusion is based in the differences of the immune system seen at birth in children who later develop allergic disease. It seems that the key-environmental trigger is the human microbiome which can change from change in diet, use of antibiotics during pregnancy, exposure to pathogenic viruses or bacteria. So highlighting the risk factors helps intervening in the right way.

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