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The Interplay between MiRNAs and LncRNAs in the Pathogenesis of Asthmatic Diseases

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Abstract

Asthma affects people of all ethnicities and ages and there has been a substantial increase in the prevalence of asthma over the past few decades, with current estimates of approximately 300 million people suffering from the disease worldwide. The initial response consists primarily of airway smooth muscle constriction and airway inflammation (oedema, inflammatory cell infiltration, increased airway secretions). Whereas more chronic responses such as structural remodelling of the airway including smooth muscle and sub-mucosal gland hyperplasia and hypertrophy, extracellular matrix (ECM) deposition and angiogenesis are generally thought to occur in parallel with inflammatory responses. Asthma is commonly associated with a Th2 response with infiltration of eosinophils, mast cells and Th2 lymphocytes into the airways, as well as elevated serum immunoglobulin IgE levels,and is determined by interaction of multiple genes and environmental factors. MicroRNAs (miRNAs) are small non-coding RNAs of 18–25 nucleotides, that have been shown to regulate gene expression at the translational level via the RNA interference pathway. In most circumstances, miRNAs are believed to either repress mRNA translation or induce the degradation of target mRNA. Since asthma is characterised by chronic inflammation of the airways, it is likely that miRNAs might be important in the pathogenesis of the disease through modulation of immune cells. Long non-coding RNAs are a heterogeneous group of non-coding RNAs with regard to origin and mechanism of action/function. Another interesting feature is that they may be expressed in both sense and antisense orientation relative to protein-coding genes. Studies demonstrated that they are regulators of different cellular processes including chromatin structure changes, transcription and post-transcriptional processing, and intracellular trafficking. The interplay between these two different types of ncRNAs is only starting to be known but appears to be very promising for a better knowledge of the asthma pathogenesis, and therefore is becoming an exciting challenge in a therapeutic perspective; this challenge will be faced by the BI(G)MED via the use of ultra-low doses of these molecules of ncRNAs in the treatment of the asthmatic disease.

Keywords: *nc RNAs, microRNAs, lnc RNAs, TH2-regulation, asthma therapy.*

Introduction

The incidence of allergic diseases in general and asthma in particular is growing in so-called industrialized countries, raising costs support higher and higher as well as a co-morbidity that is getting worse. The prevalence of asthma in different countries varies widely, but the disparity is narrowing due to rising prevalence in low and middle-income countries and plateauing in high income countries.

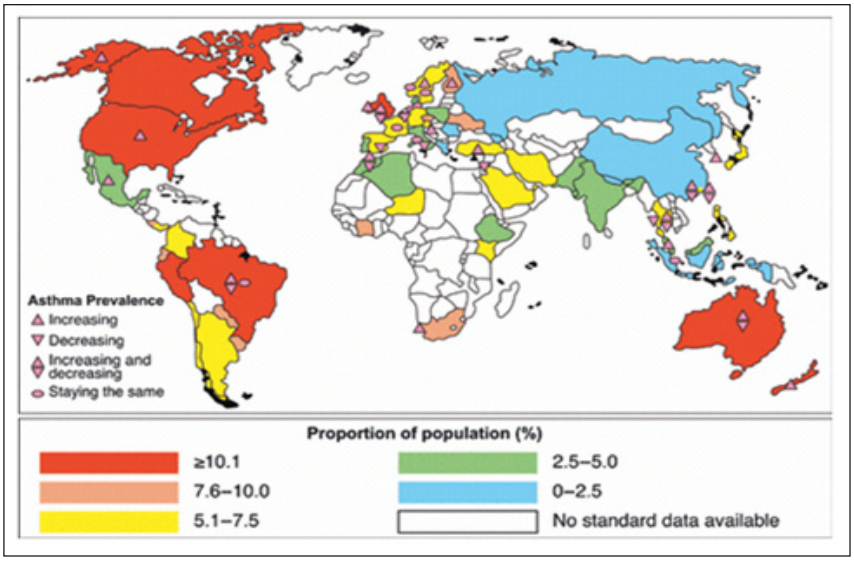

Fig 1. *Asthma Prevalence, World Health Organization Morbidity Database, 2013*

As estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease. It is estimated that the number of people with asthma will grow by more than 100 million by 2025. About 70% of asthmatics also have allergies, but occupational asthma contributes significantly to the global burden of asthma, since the condition accounts for approximately 15% of asthma amongst adults.

The prognosis of a patient with asthma currently remains dark at medium to long term, suggesting that at present there is no appropriate therapy for stabilization or recovery of chronic asthmatic condition. A possible reason for this situation is the lack of a global treatment of the asthmatic disease trying to regulate all the pathophysiological mechanisms and comorbidities involved in the development of this bronchio-pulmonary pathology.

Although it still cannot be cured, control of asthma may be achieved in the majority of patients with appropriate education, environmental control, avoidance of triggers and inducers, and individualized pharmacotherapy.[1]

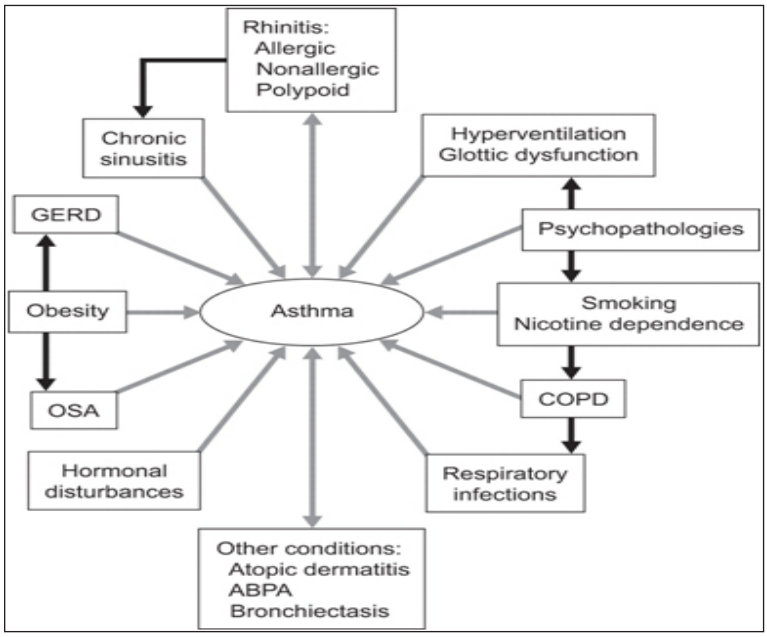

Fig 2. *Adapted from: Boulet LP. Influence of comorbid conditions on asthma. Eur Respir J. 2009; 33; GERD: gastro-esophageal reflux disease; OSA: obstructive sleep apnea; COPD: chronic obstructive pulmonary disease*

The following figure, which shows the general pathophysiology of allergic disease and asthma, somehow traces the contours of a diagnostic and therapeutic approach of holistic type.

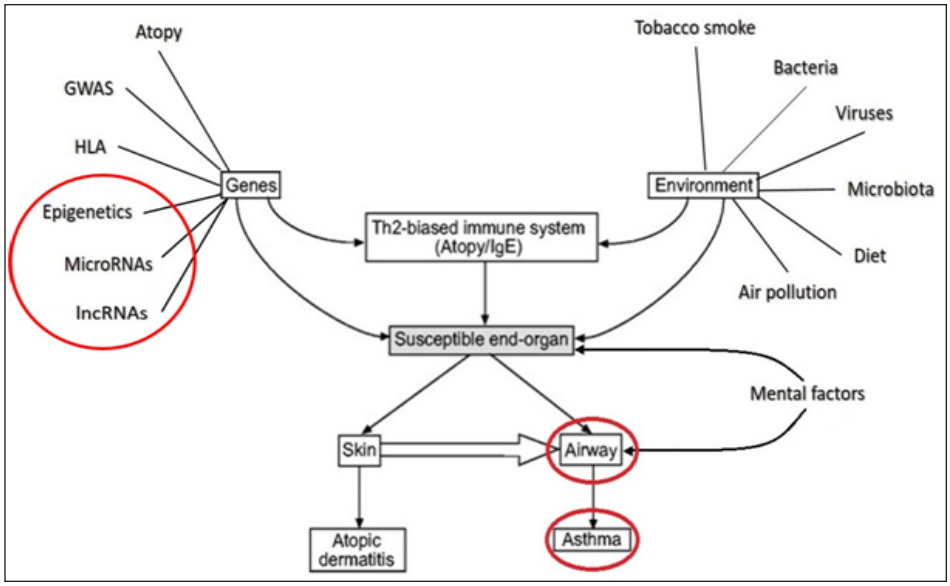

Fig 3. *General pathophysiology of allergic disease and asthma*

"Systems biology" also named "Integrative biology" is a recent and evolving interdisciplinary field that focuses on the systematic study of complex interactions in biological systems.[2]It employs a holistic approach to study all components and interactions in the network of DNA (genes), RNA, proteins and biochemical reactions within a cell or an organism. Several international consortia have already applied systems biology and network medicine approaches to asthma research; ADEPT (Airways Disease Endotyping for Personalised Therapeutics) and U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome Consortium) have, for instance, applied a clustering algorithm to two independent asthma cohorts on a small set of easily measurable clinical variables and successfully defined four longitudinally stable clusters of patients with distinct clinical and biomarker profiles (from blood, sputum and airway data).[3][4][5]

The term "P4 medicine" (Personalized, Predictive, Preventive and Participatory medicine) was coined by David Galas and Leroy Hood from the Institute for Systems Biology (ISB) in Seattle.

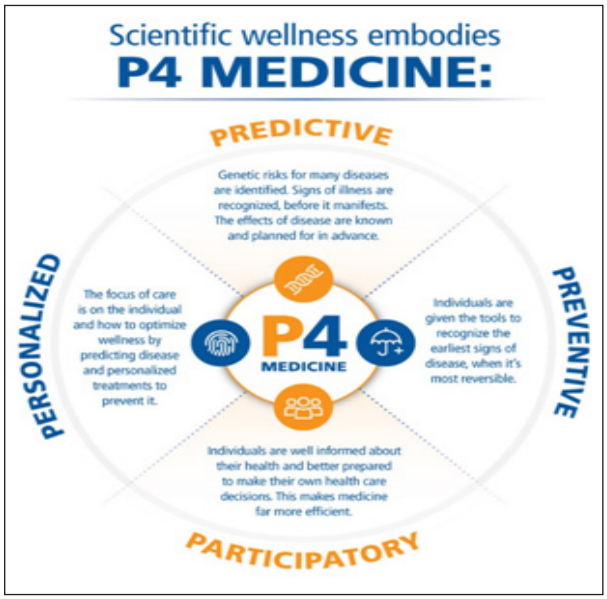

Fig 4. *P4 Medicine, Image Courtesy Providence St. Joseph Health*

Two American authors[6] have applied this concept, although innovative but of incontestable rationality, to allergic diseases in general and asthma in particular. We will follow it with a special focus on epigenomic regulation using non-coding RNAs.

Two other authors have recently described a precision medicine approach that stratifies patients based on disease mechanisms to optimize management of allergic diseases[7]. So are evoked diverse phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases, in particular asthma.

Materials and Methods

Asthma and the Epigenome

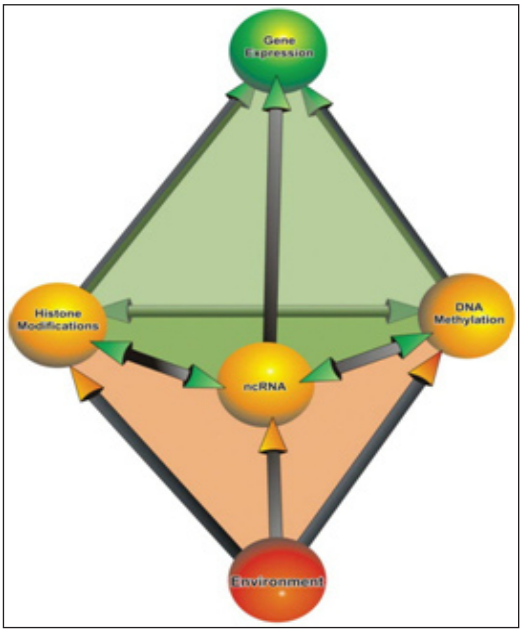

Fig 5. *Major components of epigenetic regulation in eukaryotes, Nubia AndreaVillota-Salazar & al, Journal Frontiers in Life Science Volume 9, 2016 - Issue 4*

Epigenetic mechanisms control expression levels of genes without changing DNA sequence[8].

Non-coding RNAs such as micro RNAs (miRNAs) and long intergenic noncoding RNAs (lncRNAs) are more and more viewed as a part of the epigenome as they are involved in regulation of gene expression. [9]

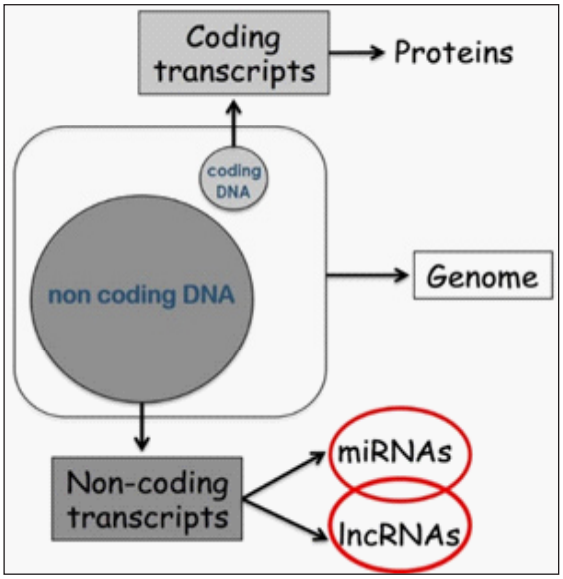

Fig 6. *Human genome organization: coding vs. non-coding transcripts*

Asthma and MicroRNAs

MiRNAs are single-stranded RNA molecules of 19-25 nucleotides in length that mediate post-transcriptional gene silencing of target genes and are highly conserved throughout evolution. A single miRNA can target hundreds of genes, and individual genes are typically targeted by multiple miRNAs, adding complexity to the network. MiRNAs can also exert global effects on gene expression by either affecting epigenetic mechanisms, such as DNA methylation or histone acetylation, or targeting transcription factors.

One approach to identify miRNAs involved in the pathogenesis of allergy is to uncover miRNAs that are differentially expressed in normal and affected tissue. Single nucleotide polymorphisms in both miRNAs and miRNA target sites have been specifically linked to asthma. But some years ago,several studies have already begun to shed light on the role that some miRNAs play in the development of allergic airway disease in animal models[10][11].

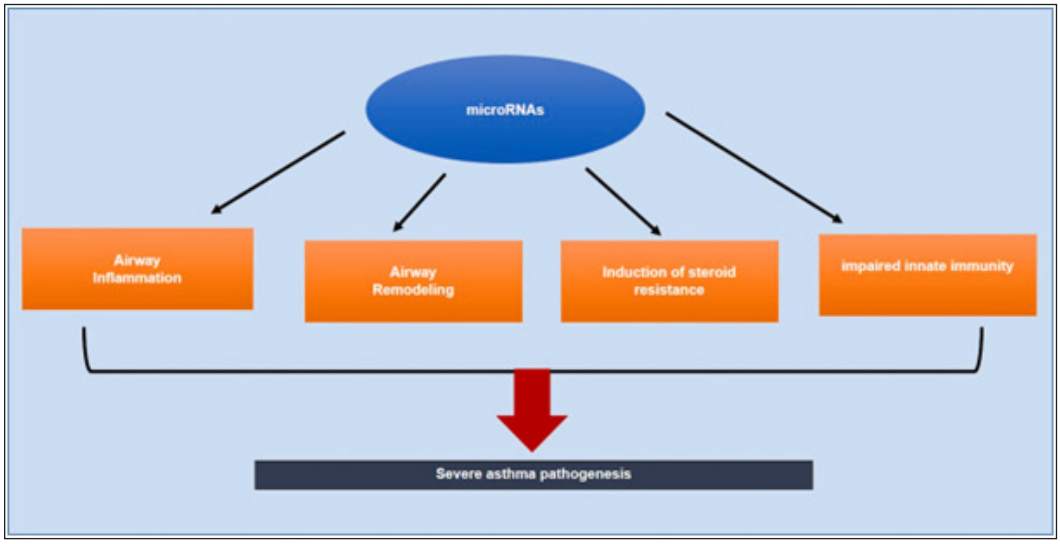

Fig 7. *Mechanisms of miRNA action involved in severe asthma pathogenesis. Maneechotesuwan K. Respir Investig. 2019 Jan;57(1)*

On a cellular level, type 2 immune responses are associated with atopic diseases, such as allergy and asthma. Airway type 2 immune responses are mainly mediated by eosinophils, mast cells, basophils, TH2 cells, group 2 innate lymphoid cells (ILC2s), Th9 cells, T regulatory (Treg) cells, and IgE-producing B cells. Critical molecular factors include the production of IgE and cytokines such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, IL-33, IL-4, IL-13, IL-5 and IL-9[12].

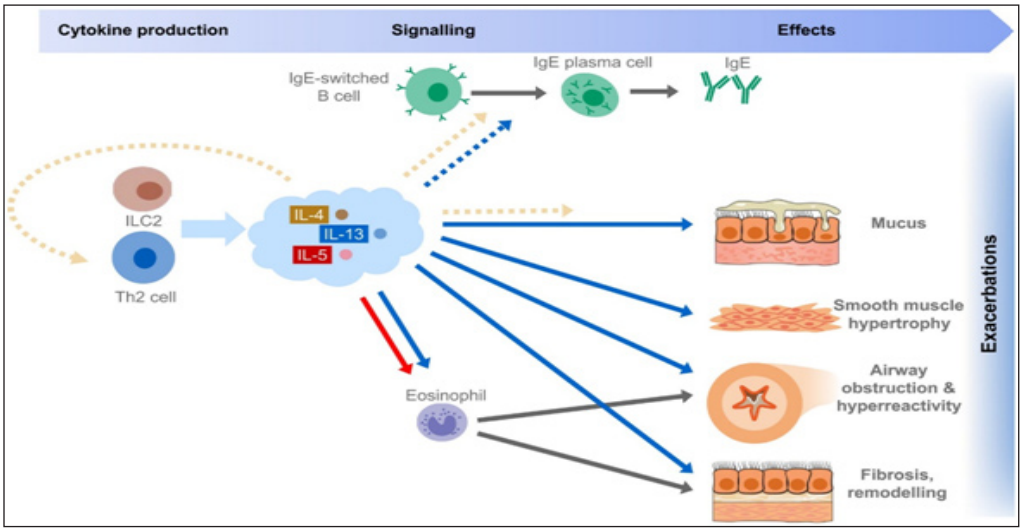

Fig 8. *overview of a type 2-driven asthma response, Robinson D. & al, Clin Exp Allergy. 2017 Feb; 47(2)*

On the basis of all these data, microRNAs will act at different levels of regulation, and we may observe:

- an expression miRNA profiling in allergic inflammation[13]
- a role of miRNAs in survival, production, and proliferation of type 2 immune cells[14]
- and in M2 polarization as well [15]

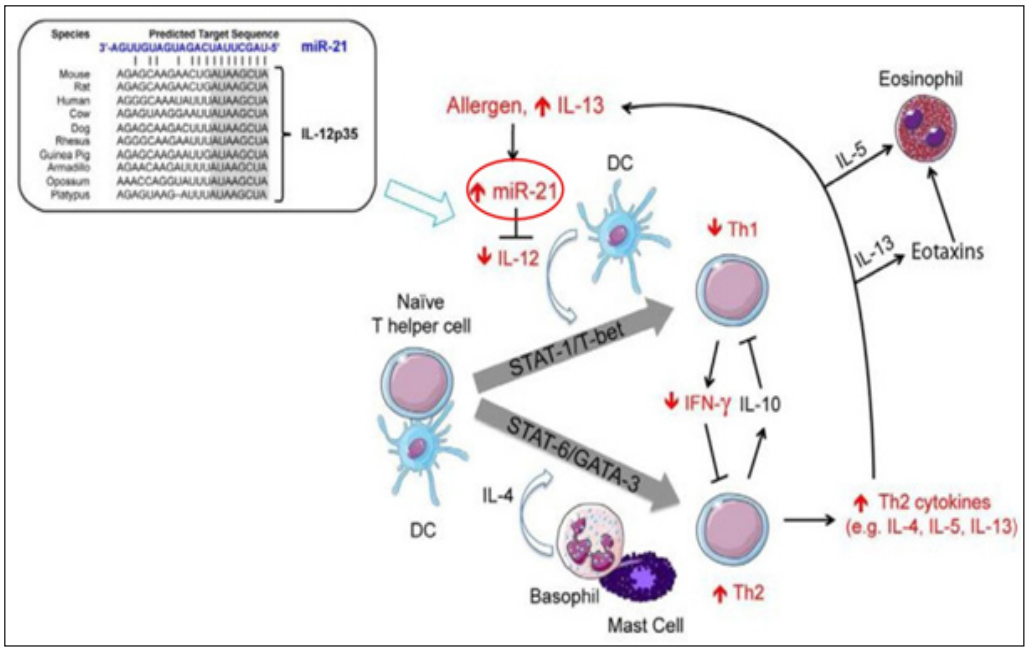

Fig 9. *regulation of the adaptive immune system by miR-21 in allergic inflammatory responses, Liu F & al, Mol Med Rep. 2012 Nov;6(5)*

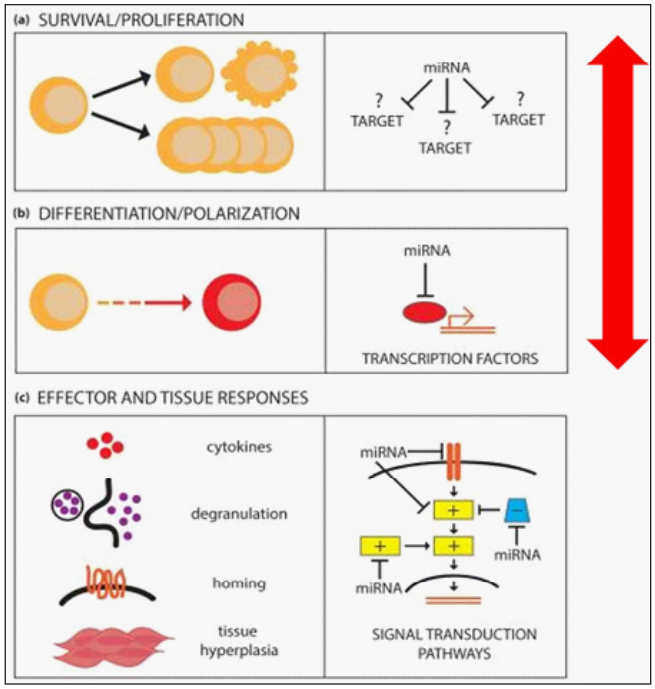

Fig 9. *miRNAs multifaceted regulation of type 2 cell function; Pua HH, Ansel KM. Curr Opin Immunol. 2015 Oct;36*

Studies in multiple cell types, diseases and model systems have shown that individual miRNAs can positively or negatively regulate allergic responses, often through the modulation of key signaling pathways in type 2 effector responses.

Asthma and Long Non-Coding RNAs

LncRNAs are non-coding RNAs that are more than 200 nucleotides in length. They have been identified to have functional roles in a diverse range of cellular functions such as development, differentiation, cell fate, as well as disease pathogenesis[16].

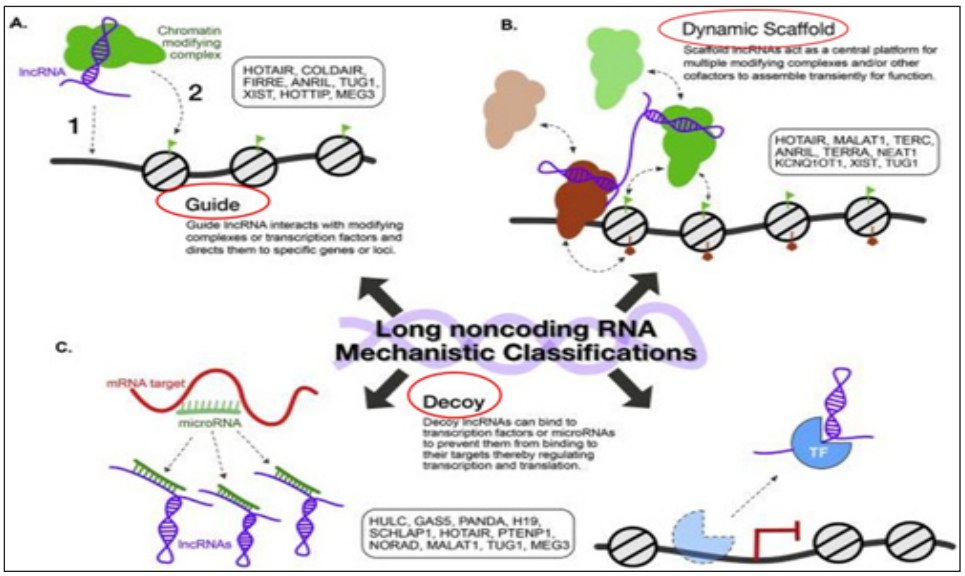

Fig 10. *General mechanisms for lncRNA classification. Balas MM & Johnson AM. Noncoding RNA Res. 2018 Mar 31;3(3)*

LncRNAs are involved in the development of multiple diseases, including asthma[17] through transcriptional or post-transcriptional regulation of protein expression through various mechanisms. Unlike cancer, where studies abound, research about lncRNAs did not pay much attention to the relationship between these large noncoding RNAs and asthma. There are nevertheless some interesting works on this subject.Thus, for example, the M PERRY group in London, was able to demonstrate the regulatory action of the asthmatic phenotype of long noncoding RNA Plasmocytoma Variant Translocation 1 (lnc PVT1), which is only increased in the primary Airway Smooth Muscle Cells (ASMCs) of patients with severe asthma, where it decreases IL-6 production and cell proliferation [18].

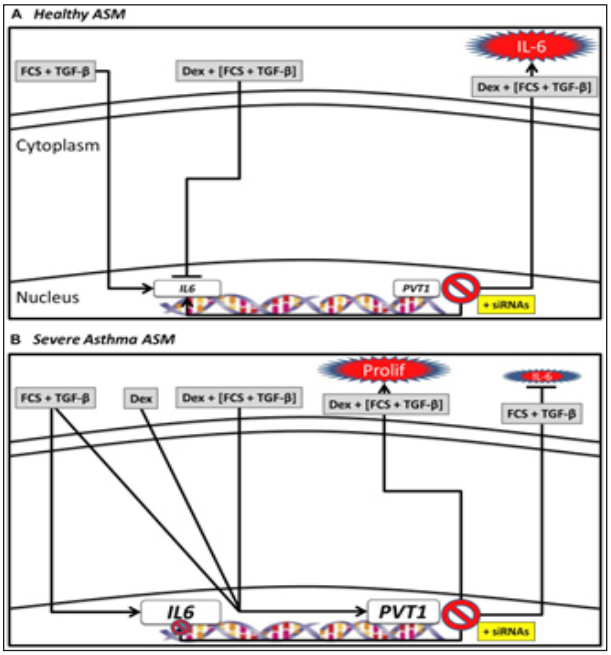

Fig 11. *Potential mechanisms for PVT1 contribution to ASMC proliferation and IL-6 release in asthmatic patients.M M Perry & al, J Allergy Clin Immunol. 2017 Mar; 139(3)*

Another group was able recently to highlight a similar role of lnc GAS5 by demonstrating the important role played by the long noncoding RNA Growth Arrest-Specific transcript 5 (lncRNA GAS5) / miR-10a / BDNF regulatory axis in promoting ASMCs proliferation, thus contributing to asthma.[19]Youngest studies show that lncRNAs are involved in different phenotypes of asthma, and especially lnc_000127 may be effective for reducing Th2 inflammation in Eos asthma.[17]

As the conductor controls the elements of musical expression (tempo, dynamics, articulation) so finally lncRNAs orchestrate and modulate gene expression and cellular functions.

Discussion

A group of clinical physicians and myself conducted a six-months study published in 2018 [20], which showed the positive regulatory effect allowing a partial or complete replacement of a prolonged corticotherapy in asthma by an immunogenetic nanotherapy.

The general principle is to use for therapeutic purposes the largest possible number of microRNAs and lncRNAs, whose involvement in the pathophysiology of asthma has been validated through the research. In order to comply with the principle of biomimetics, we use nanodoses located between nanograms and femtograms or even lower, whose action will be driven according to the general principle of Hormesis, that corresponds to the so-called "dose-response concept", which represents the biological integration of how living systems at all levels of organization, from the cell to the individual, respond, adapt or fail to adapt to endogenous agents, metabolic processes, and externally imposed stressors/threats.[21]

At present, the referenced nanotransporter is xylitol, but we are developing a more efficient lipid carrier in a near future.

The results of our study showed that after six months nearly two-thirds of the patients were able to reduce significantly or stop definitively their previous corticotherapy.

Conclusion

In asthma

- miRNAs regulate allergic inflammation.
- miRNAs act coordinately through target gene networks.
- miRNAs impact diverse cellular functions in type 2 immune cells.
- miRNAs provide novel biomarkers and therapeutic strategies.
- lncRNAs also regulate allergic inflammation.
- lncRNAs act coordinately to decrease ASCMs proliferation.
- lncRNAs thus provide novel therapeutic strategies.

Ultra-low doses of molecules are capable of having an effective regulatory effect on the cellular structures involved in allergic diseases, especially asthma.It is therefore possible to treat a chronic and sometimes very unpleasant disease such as asthma over the long-term without having to fear any adverse effects.

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