OPINION ARTICLE

Towards precision medicine: The application of omics technologies in asthma management [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Asthma is a chronic obstructive respiratory disease characterised by bronchial inflammation. Its biological and clinical features have been widely explored and a number of pharmacological treatments are currently available. Currently several aspects of asthma pathophysiological background remain unclear, and this is crucial for the traditional asthma phenotype approach as well as for new endotype definition. In this scenario, the identification of new molecular and clinical biomarkers may be helpful in order to better understand the disease, define specific diagnostic tools and highlight relevant novel targets for pharmacology treatments. Omics technologies offer an innovative research tool for addressing the above mentioned goals. However, there is still a lot to do both in the fields of basic research and in the clinical application of these new technologies. Recently, genome-wide association studies, microRNAs and proteomics are contributing to enrich the available data for the identification of new asthma biomarkers. A precise approach to the patient with asthma, particularly with severe uncontrolled asthma, requires new and specific therapeutic targets, but also proper tools able to drive the clinician in tailoring the treatment. On the other hand, treatment response predictors are needed, particularly in the field of biological drugs, whose sustainability implies a correct and precise patient selection. Translating acquired knowledge about omics in clinical practice may address the unmet needs described above, but large-scale studies are required in order to confirm omics relevance and effectiveness in daily practice. Thus in our opinion the application of omics is still lagging in the real-life setting.

Open Peer Review

Approval Status

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version 2 (revision) 18 May 2018		 view
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version 1 04 Apr 2018		

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Severe asthma, Omics sciences, Inflammation, Precision medicine

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Introduction

Several aspects of asthma heterogeneity both from a clinical and pathophysiological perspective still remain unclear. A number of treatment options have been developed over time, from the widely used corticosteroids to personalized approaches, including recently introduced biological therapies. The new classification of severe asthma is based on endotypes, whose definition relies on the features of the underlying inflammation. The endotypes define traditional phenotypes by describing their pathophysiological mechanisms^{1,2}. Exploring endotypes and phenotypes supports the identification of specific molecular targets, which can be addressed by precision treatments such as biologic drugs. The management of severe asthma is benefitting from personalized medicine approaches based on the characterization of an increasing number of endotypes, which represent the targets of specific therapies³. These are mainly represented by the Th2-high subtype and the Th2-low subtype, characterized respectively by the presence of eosinophilic or neutrophilic/paucigranulocytic airway inflammation³. Currently targeted therapies for a number of Th2 – low endotypes are still lacking⁴. For this and other reasons, the need for increasing the effectiveness of personalized therapies opens the field to the omics approach.

New asthma phenotyping has led to a growing interest in targeted therapies. The search for new pharmacological targets has caused interest in understanding the pathophysiological and molecular mechanisms underlying asthma. So far, the majority of the available drugs target the Th2-cytokine pathway⁵.

What else could be done for the management of severe asthma

Omics technology supports precision medicine in identifying the most effective treatment for different clinical phenotypes, in contrast with the “one size fits all” approach. Indeed, omics sciences contribute to the definition of new biomarkers, which can be useful as hallmarks of a specific asthma endotype or phenotype, and relevant as novel targets for pharmacology treatments. In the field of molecular biology, omics is a neologism that indicates high-throughput experimental technologies providing the tools for comprehensively monitoring the disease processes at a molecular level. The suffix “ome” comes from “chromosome” and currently includes several biological fields such as genomics, transcriptomics, proteomics, metabolomics and epigenomics. Genomics and transcriptomics have been used to identify genes associated with asthma severity (Figure 1). Recent genome-wide association studies (GWAS) have shed

Figure 1. A systems biology approach: From omics science to precision medicine.

light on distinct pathways that contribute to asthma inflammation. Genes such as HLA, IL13, IL33, thymic stromal lymphopoietin (TSLP) involved in Th2 pathway, IL-1 receptor-like 1 (IL1RL1), encodes ST2, and the receptor for IL-33 are associated with asthma onset. In contrast, it is well-known that the risk of childhood asthma is associated with the 17q21 locus encoding the ORMDL3 and GSDML genes^{6,7}. Transcriptomics are focused on microRNAs (MiRNAs). MiRNAs are small non-coding single strand RNA chains involved in post-transcriptional regulation processes. MiRNAs play a key role in regulating cell functions as well as in modulating the inflammatory pathways. They may influence the single endotype profile in the complex asthma phenotype picture. MiRNAs can be collected through peripheral blood sampling, or, more invasively, through bronchial biopsies and induced sputum^{8,9}. Under-expression of miRNA 192 in blood was investigated in a small study, in which asthma patients underwent an allergen inhalation challenge¹⁰. The relevance of miRNA as a biomarker is increasingly investigated. Different levels of miR-1248 serum expression in asthmatic vs non-asthmatic patients have been documented. In asthmatic patients miR-1248 is also involved in the regulation of IL-5 pathway¹⁰. Among the omics, circulating miRNA deserves a specific interest. Circulating miRNAs might be a non-invasive biomarker useful in asthma diagnosis and characterisation, as demonstrated in a recent study. According to the authors, a specific subset of circulating miRNAs (miR-125b, miR-16, miR-299-5p, miR-126, miR-206, and miR-133b) was found in patients with allergic rhinitis and asthma¹¹.

Epigenomics represent another relevant issue. The “methylome” (the set of DNA methylation patterns) has been increasingly investigated through highly sophisticated sequence-based assays. Epigenetic mechanisms could lead to the identification of new asthma biomarkers. Recently, an epigenetic association between serum IgE concentration and methylation at different loci derived from DNA of leukocytes has been described. Methylation at these CpG islands differed significantly in isolated eosinophils between subjects with and without asthma and high IgE levels¹².

Modern and advanced technologies, such as mass spectrometry, allow the detection of several proteins involved in the inflammatory mechanisms of asthma. Among the proteomics signatures characterized so far, Galectin-3 deserves to be mentioned. It has been demonstrated that this protein is expressed in omalizumab responders only. Furthermore galectin-3 seems to be associated with a more evident respiratory function improvement in asthmatic patients treated with omalizumab¹³.

The increasing interest in metabolomics, is mainly due to its prospective clinical applications. According to recent findings it is possible to define the metabolic profile through different samples including exhaled breath, urine, plasma and serum¹⁴. Currently a branch of metabolomics called “breathomics” focuses on volatile organic compounds (VOCs) from the respiratory tract. VOCs represent potential non-invasive metabolic biomarkers, particularly in the diagnosis and monitoring of pulmonary diseases including asthma¹⁵. Moreover, an electronic nose able to discriminate asthmatic from healthy controls by detecting different VOCs in exhaled breath has been developed^{15,16}. Therefore, metabolomics could play a key role in identifying biomarkers and improving asthma endotyping.

Conclusion

The application of omics technology in asthma is following other research fields, such as oncology¹⁷. Similarly, monoclonal antibodies (mAbs) for severe asthma have been recently introduced, while biological therapies addressing rheumatic diseases, solid tumors and blood cancer arrived more than a decade before. From 2006 to 2017 omalizumab was the only available treatment for severe allergic asthma. Only in recent years research and knowledge on new drugs has been developed to achieve new and more effective therapeutic options¹⁸. Though an increasing interest in omics technology, none of the omics signatures mentioned above have been translated into clinical practice. We believe that there is an urgent need for large-scale studies. Particularly, specific Randomized Controlled Trials would be necessary to definitively confirm the clinical relevance of omics and reinforcing omics' role in searching for new biomarkers and prognostic factors. The need for correctly selecting the right mAb for the right patient is one of the key points in severe asthma management. The real challenge for researchers and clinicians in the “omics era” is therefore translating acquired knowledge into clinical practice in order to emphasize omics' role in precision medicine and to predict response to treatments. Unfortunately, in our opinion we are still far from that scenario.

Data availability

No data is associated with this article.

Competing interests

No competing interests were disclosed.

Grant information

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Bronchial asthma is a complex and heterogeneous pathology due to multiple mechanisms that are not present in all patients at any given time-point, or in the same patient at different time-points.

Furthermore this disorder is not characterized by a single biomarker, but by a panel of biomarkers which describe its molecular aspects.

In the last years, "omics" sciences have improved disease phenotyping by linking the molecular mechanisms to the clinical field.

In their opinion article Scelfo and colleagues discussed about the application of omics sciences in the asthma characterization.

The topic is very interesting although I have some concerns regarding some aspects of the article:

Firstly, the main concept of omics sciences, such as epigenomics and metabolomics, should be explained in a more extensive manner.

Furthermore, several other proteins other than galectin- 3 are associated to severe asthma. I suggest to include other examples.

Other matrixes (please prefer matrix to sample) have been used to metabolomics analysis in asthma such as exhaled breath condensate. This part should be extended, considered recent findings on the possibility to phenotype asthmatic patients using this method.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 24 April 2018

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The heterogeneity and complexity of the asthma syndrome necessitates a different approach to its management. The use of clinical features and physiological and inflammatory data is no longer sufficient. Omics data and clustering will provide a greater chance of phenotyping asthma according to the mechanisms driving the disease in each phenotype, from which a composite set of biomarkers could be used to define and categorise the endotypes. This will help to develop personalised medicine for asthma that will allow for more precise treatment and also provide a source of novel targets and hence new treatments for each defined endotype. It is high time that personalised medicine be applied to the whole spectrum of asthma.

The application proposed by the authors is very promising, because it allows a precise phenotyping of asthmatic patients and a correct choice of therapeutic agents, in particular as regards the treatment with biologicals.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: I've received grants as speakers by GSK, Novartis, Astrazeneca, Biofutura, Menarini, Guidotti

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 08 May 2018

Chiara Scelfo, Azienda USL di Reggio Emilia, Reggio Emilia, Italy

Dear Dr. Micheletto,

We thank you for agreeing to review our manuscript. We also thank you for your valuable and positive comments. This is an incentive for us to try to improve our work.

My best regards,
Chiara Scelfo and coworkers

Competing Interests: No competing interests were disclosed.

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