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NARRATIVE REVIEW

Translational medicine and omic sciences in pediatric pulmonology

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ABSTRACT

During the past two decades omic technologies have been gaining importance in the field of complex non-communicable diseases. Asthma is a condition particularly suited to be studied with this approach since it is a multifactorial disease resulting from a complex interplay between genetic, biological, and environmental factors.

Aim of our narrative review is to summarize the findings of the most recent literature on the application of omic technologies in the study of asthma in children.

The identified studies belong to two main research areas: the first concerns the prediction of recurrent wheezing/asthma development; the second concerns the assessment of children with asthma to study the molecular mechanisms underlying relevant clinical features of the disease and to search for biomarkers predictive of treatment response. The identified studies show the potential of omic platforms but also the need of integrating omic and clinical data in the view of possible clinical applications in a near future.

IMPACT STATEMENT: Our narrative review provides a general overview on the main findings of the most recent studies that have applied a omic approach in the study of pediatric asthma.

KEY WORDS

Asthma; children; transcriptomics; metabolomics; microbiomics.

INTRODUCTION

In the past two decades a growing number of studies in pediatric pulmonology have applied *omic* sciences to investigate respiratory disease pathobiology through an unbiased approach, not guided by any a-priori hypothesis. Omic sciences, in fact, are disciplines that study molecules with similar characteristics (for examples peptides, RNAs, metabolites) applying a comprehensive approach based on the use of high-throughput analytical platforms. The management and analysis of the obtained large-scale biomolecular data require the application of sophisticated tools for multivariate statistical analysis that enable the identification of molecular profiles associated with a condition of interest. The final objective for omic sciences, in fact, is the improvement of our ability of diagnose and treat diseases thanks to a better understanding of the underlying pathobiological mechanisms (1).

Asthma is a condition particularly suited to be studied with this approach since it is a multifactorial noncommunicable disease which results from a complex interplay between genetic, biological, and environmental factors (2).

Aim of the present manuscript is to narratively review the papers published in the past 5 years that involve the application of *omic* technologies in the study of asthma in children (**Figure 1**).

MEDLINE/Pubmed database was searched using the following terms: “asthma” and “metabolomics” or “transcriptomics” or “proteomics” or “metagenomics” or “microbiomics”. Filters applied were: language (English), date of publication (from 2018 to 2023) and age of study subjects (0-18 years).

The identified studies belong to two main research areas: the first concerns the prediction of recurrent wheezing/asthma development in children, the second concerns the assessment of children who already have a diagnosis of asthma.

ASTHMA PREDICTION

One of the main challenges in the field of pediatric asthma is the prediction of asthma development and the study of the relationship between recurrent wheezing and asthma (**Table 1**).

Some authors have investigated whether molecular features predictive of asthma development may be identified in the early stages of life. Different research groups (3, 4) demonstrated that the metabolomic urinary profile in the first days or weeks of life is associated with recurrent wheezing and asthma development, suggesting that an innate metabolic dysregulation could play a role in subsequent development of this condition. A significant association was also described between serum lipidomic profile at 6 months of age and the development of recurrent wheezing in preschool age but not with the diagnosis of asthma at the age of 6 (5).

From a microbiomic standpoint, in a population-based birth cohort an early nasal microbiota profile characterized by early Moraxella sparsity and subsequent increase was found to correlate with the development of asthma (6). In the same population the authors demonstrated an association between the use of antibiotics during the first 2 years of life and the diagnosis of asthma at 7 years of age (7), showing that such relationship was partially mediated by longitudinal changes in nasal microbiota, underscoring therefore the role of upper airway microorganism profile in asthma pathobiology.

In addition, a recent systematic review has summarized the available data on the possible association between the gut microbiota during early life and the following development of respiratory problems, including wheezing and asthma (8).

Several studies have applied an *omic* approach to study the relationship between acute bronchiolitis in

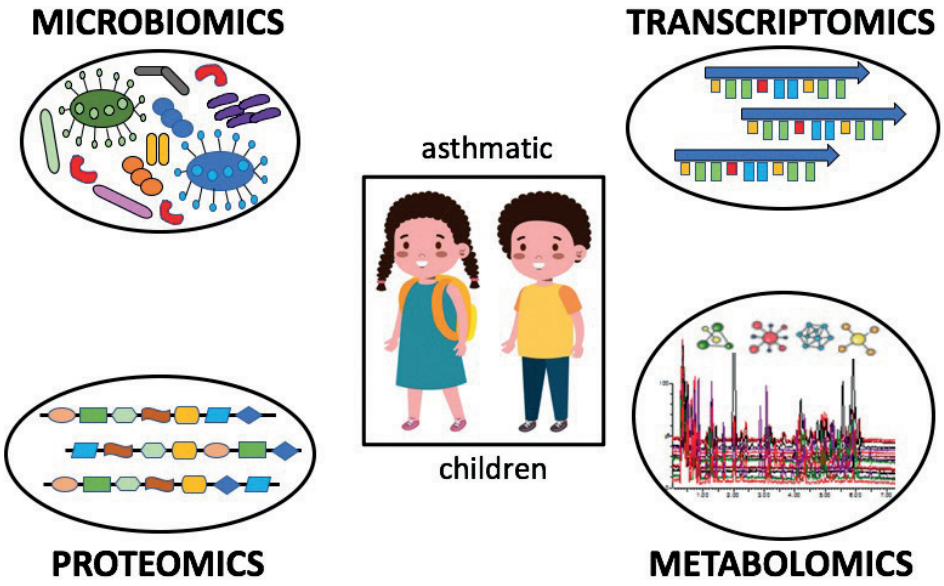

Figure 1. *Schematic representation of the omic technologies applied to pediatric asthma as discussed in the manuscript.*

Table 1. *Studies investigating the role of omic approaches in early prediction of asthma development.*

References	Population	Omic approach	Biologic matrix	Main results
Carraro *et al.* (2)	Newborns in the first days of life	Metabolomic analysis	Urine	Association between metabolomic profile at birth and recurrent wheezing not preceded by bronchiolitis
Chawes *et al.* (3)	Newborns 4 weeks old born to asthmatic mothers	Metabolomic analysis	Urine	Association between metabolomics profile and early onset asthma
Rago *et al.* (4)	Infants evaluated at 6 months of age and re-assessed at 6 years of age	Lipidomic analysis	Plasma	Association between lipidomic profile at 6 months of age and asthma before the age of three
Toivonen *et al.* (5)	Birth cohort assessed at 2,13 and 24 months of age	Microbiomic analysis	Nasal swab	Association between early microbiomic profile and asthma development at 7 years of age
Barlotta *et al.* (8)	Infants with acute bronchiolitis (age <12 months)	Metabolomic analysis	Urine	Association between metabolomic profile and recurrent wheezing during the 2 years following acute bronchiolitis
Zhu *et al.* (9) Fujiogi *et al.* (10) Ooka *et al.* (11) Mansbach *et al.* (12) Zhu *et al.* (13)	Infants hospitalized for acute bronchiolitis (age <12 months)	Metabolomic, lipidomic, proteomic, transcriptomic, microbiomic analysis	Nasal swab	Association between *omic* profiles and recurrent wheezing/ asthma

infancy and the subsequent development of recurrent wheezing and asthma.

A study from our group (9) demonstrated that among children with bronchiolitis those who present with 3 or more wheezing episodes in the following two years could be discriminated according to their metabolomic urinary profile during acute infection.

A significant contribution to the understanding of the mechanistic relationship between bronchiolitis and recurrent wheezing/asthma has been recently provided by the 35th Multicenter Airway Research Collaboration (MARC-35) study that included 921 infants younger than 1 year hospitalized in 17 centers across USA for acute bronchiolitis during 3 epidemic seasons from 2011 to 2014. At recruitment nasopharyngeal airway specimens were collected and then analyzed through several *omic* approaches to evaluate the relationship between the nasopharyngeal molecular profiles and the diagnosis of both recurrent wheezing during preschool years and asthma at the age of 6.

The authors demonstrated that children who later developed asthma, during acute viral bronchiolitis showed a characteristic metabolomic and lipidomic nasopharyngeal profile enriched in aminoacids and lysophosphatidylcholine and with low levels of polyunsaturated fatty acids (PUFA) (10, 11). Also, the proteomic analysis of nasopharyngeal samples, together with clinical and virological data, enabled the characterization of a cluster of infants at higher risk of developing asthma (12). Longitudinally analyzing the nasopharyngeal microbiota, the authors also found that a relative abundance of *Moraxella* and *Streptococcus* species in the post-hospitalization period was associated with a significantly increased risk of recurrent wheezing at 3 years of age (13). To further investigate the possible causal relationship between microbic profile and asthma, the authors, applying a dual transcriptomic approach (metagenomics and transcriptomics) together with a metabolomic approach, were able to describe an interplay among microbial profile and host response which likely contributes to asthma development (14).

Moreover, considering children according to viral etiology, through an integrated analysis of clinical and *omic* data the authors could identify a cluster of children with significantly higher risk of recurrent wheezing and asthma within both the subset of infants with Respi-

ratory Syncytial Virus (RSV) bronchiolitis (15) and the subset of infants with Rhinovirus (RV) (16).

Taken together these studies suggest that the integrated analysis of clinical data together with a limited number of biomarkers, characterized through *omic* technologies, could guide the identification of children with acute bronchiolitis more likely to develop recurrent wheeze and asthma.

ASTHMA ASSESSMENT

Considering children who already have a diagnosis of asthma, *omic* approaches have been used to investigate the molecular processes associated with specific clinical features of the disease, such as asthma severity or symptom pattern overtime (**Table 2**).

Some papers have investigated the association between upper airways microbic profile the and the risk of acute exacerbation or loss of symptom control.

A recent report of a workshop titled "Microbiome, Metabolism and Immunoregulation of Asthma" (17) held by the "American Thoracic Society" and the "National Institute of Allergy and Infectious disease" underlined the role of upper airway microbial composition as a protective or risk factor for asthma exacerbation.

In school age children with well-controlled asthma, it was demonstrated that an upper airway microbiota dominated by *Corynebacterium*/*Dolosigranulum* was associated with lower risk of losing asthma control compared to microbiota profiles dominated by *Staphylococcus*, *Moraxella* and *Streptococcus* (18). Likewise, McCauley *et al*. (19), analyzing several nasal secretion samples collected in asthmatic children during fall season, demonstrated that distinct microbiota profiles can be described, and that higher abundance of Moraxella species was associated with higher risk of acute asthma exacerbations. In a further study the authors integrated data derived from the analysis of upper airway microbiota and the analysis of nasal transcriptomic profile showing an interaction between specific bacteria networks and gene expression that might influence the risk of acute exacerbations (20).

Finally, a study which simultaneously applied a microbiomic and a metabolomic approach, demonstrated that in preschool children with a doctor-based diagnosis of asthma, fecal metabolic profile correlated with the frequency of wheezing, a relationship which was independent from the microbic arrangements (21).

The molecular signature associated with exacerbation rate has been also evaluated though a metabolomic approach. In 4 cohorts of asthmatic children with exacerbation prone asthma (*i.e*. more than 3 exacerbation per year) a blood metabolomic arrangement with perturbed levels of arginine, lysine and methionine was reported (22).

As for asthma severity, metabolomics has been considered by many research groups a valuable tool to understand the disease pathogenetic mechanisms, especially those involved in severe asthma. Although no new articles have been published in the past 5 years, earlier studies, applied to both blood and exhaled breath condensate, demonstrated the potential role of this approach in the characterization of the biochemical-metabolic patterns associated with severe asthma in children (23-25). These previous papers suggest that increased oxidative stress and possibly a lack of vitamin D-related metabolites might have a role in the pathobiology of severe asthma.

Table 2. *Studies investigating the role of omic approaches in the assessment of children with asthma.*

References	Omic approach	Biologic matrix	Main results
Zhou *et al.* (17) McCauley *et al.* (18)	Microbiomic analysis	Nasal swab	Association between microbiomic profile ad risk of asthma loss of control or exacerbation
Cottrill *et al.* (21)	Metabolomic analysis	Blood	Association between metabolomic profile and exacerbation-prone phenotype
Fitzpatrick *et al.* (22) Park *et al.* (23) Carraro *et al.* (24) Do *et al.* (26) Goldman *et al.* (27)	Metabolomic, transcriptomic, microbiomic analysis	Blood Exhaled breath condensate (EBC) Bronchoalveolar lavage (BAL)	Association between omic profiles and asthma severity
Carraro *et al.* (29)	Metabolomic analysis	Urine	Association between metabolomic profile and response to biologic therapy in severe asthma

Regarding transcriptomics, the analysis of gene expression of peripheral blood mononuclear cells demonstrated a profile indicative of activation of TH1/TH17 pathway in children with severe asthma (26). In addition, a recent study (27) evaluated nasal transcriptomics showing that children with severe persistent asthma are characterized by a group of master regulatory genes (LRRC23, TMEM 231, CAPS, PTPRC, and FYB), many of which are involved in ciliary function and airway inflammation. These interesting findings pave the way to targeted studies to further investigate the role of these genes in severe asthma pathobiology. Finally, a microbiomic approach was applied to samples of bronchoalveolar lavage to study the microbiota of lower airways in children with severe asthma. The authors found 15 bacterial genera and 7 fungal genera which discriminate severe asthmatic children from non-asthmatic children (28).

In the assessment of asthma an important role for unbiased *omic* approaches is also in the identification of possible molecular signatures associated with the response to therapy (**Table 2**). Such research area is of the utmost importance in as much as it may lay foundation for the development of a truly personalized therapeutic approach based on the a-priori identification of the patients more likely to benefit from a specific treatment. The chance of developing such a targeted therapeutic strategy is particularly appealing for the management of severe asthma.

Many studies have investigated this field by applying a genomic approach to analyze the effect of genetic variants on the patient's response to treatment. The potential of this approach, named pharmacogenomics, has been recently and nicely reviewed elsewhere (29). In addition, some studies are proposing the use of other *omic* platforms to identify, among asthmatic patients, the responders to a specific drug. Recently a multicenter Italian study (30) demonstrated, in children with severe asthma, an association between the baseline urinary metabolomic profile and the clinical response to the anti-IgE monoclonal antibodies omalizumab. Urine samples collected before starting the treatment were analyzed through a mass spectrometry (MS)-based metabolomic approach that enabled the discrimination of responders from non-responders, being the former characterized by higher levels of dipeptides and amino acids.

CONCLUSIONS

For the past two decades *omic* technologies have been playing a growing role in the field of complex non-communicable diseases like asthma. Here we summarized the most recent studies applying these platforms in pediatric asthma. Taken together these studies underline the potential of *omic* platforms together with the need of integrating *omic* and clinical data in the view of possible clinical applications. O*mic* findings, indeed, need to be validated beyond the populations in which they were first reported and to be confirmed through target approaches before being ready for clinical use. Nonetheless, in a near future, an integrated clinical-*omic* approach could help physicians in the prediction of asthma, in the characterization of children with more severe disease and in the identification of those more likely to benefit from a specific treatment. More broadly, this integrated clinical-*omic* approach has a potential for guiding the identification of high-risk subgroups of children who deserve closer follow-up or the development of new targeted preventive strategies and treatment approaches.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authorship

Drs. Silvia Carraro, Stefania Zanconato, Valentina Agnese Ferraro.

Author contributions

SC wrote the first draft, SZ and VAF critically revised the manuscript.

Ethical approval

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N/A.

Data sharing and data accessibility

No original data are presented in the manuscript.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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