8 OMICS

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KEY MESSAGES

- Omics represents a key tool for precision medicine
- New biomarkers will allow better diagnosis strategies
- Integration of omic and clinical data will lead to personalised medicine
- Deeper knowledge of the mechanisms underlying allergy and asthma will converge into novel patient management approaches

Omics technologies are based on the acquisition and analysis of a large data volumes, using fast and automated high-performance methods. They have brought along a paradigm shift in the development of research strategies. Genomics, Epigenomics, Transcriptomics, Proteomics and Metabolomics are by now widely applied to identify biological variants, to characterize complex biochemical systems, to study pathophysiological processes and to define new biomarker strategies (Figure 1). Each omics discipline provides different information on the regulation of gene expression in health and diseases such as asthma (Figure 2).

GENOMICS

Genomics is the study of the DNA and its associated alterations of a specific tissue/cell. Genomic studies in asthma focused on candidate gene approaches (specific genes linked to asthma outcomes). In 2007, the first genome-wide association study (GWAS) enabled the detection of previously undescribed genes. Today, 38 loci have been associated with asthma; among these, 17q12-21 is the most consistent cluster of genes. This locus harbours the *ORMDL3* (orosomucoid-like 3) and *GSDMB* (gasdermin B) genes, underlying airway remodeling and responsiveness in asthma.

EPIGENOMICS

Epigenetic modifications consisting of DNA methylation and post-translational histone modifications contribute to the control of gene expression by modulating DNA accessibility and protein interactions. They can therefore mediate the interaction with the environment, also in the context of asthma. In a series of epigenome-wide association studies (EWAS), differentially methylated CpGs associated with asthma were identified, with stronger effects, better correlations with gene expression changes and increased reproducibility when nasal epithelial cells rather than blood samples were used.

TRANSCRIPTOMICS

Transcriptomics is the science that studies the transcriptome, i.e. the sum of all RNA transcripts present in one or a population of cells (mRNA, rRNA, tRNA, miRNA and other non-coding RNAs). As the transcriptome is different among cell populations and varies with environmental conditions, choosing the appropriate sample compartment and disease phenotypes are key elements for transcriptomic analyses. Analysing the transcriptome of different biological samples (sputum, nasal brushings, and endobronchial brushings/biopsies) in the U-BIOPRED project identified a set of differentially expressed genes (DEG) associated with asthma severity that could be potential biomarkers.

PROTEOMICS

Proteomics approaches range from high-throughput mass-spectrometry based methods that mainly identify more abundant proteins, to targeted methods focused on smaller sets of proteins such as Western blotting or multiplex assays (Luminex, Simoa, OLINK, etc.). Proteomics can capture molecular information on proteotypes that cannot be retrieved otherwise, e.g. on post-translational modifications, protein interactions and localization. In a proteomics study using asthma patient's sputum, molecular subphenotypes were identified corresponding to the known eosinophilic, neutrophilic and atopic asthma phenotypes, and further studies are expected to yield more information.

METABOLOMICS

Metabolomics focusses on the study of compounds defined as metabolites that encompass the metabolism of a living organism/tissue/cell. Characterization of the metabolic profile has the potential to capture metabolic alterations in asthma and has revealed alterations in cellular energy, amino acid, oxidative stress, fatty acid, sphingolipid and phospholipid metabolism. For example, the lipid mediator sphingosine-1-phosphate (S1P) regulated by ORMDL3 has been associated with increased bronchiolitis severity, and nitric oxide (NO) with airway inflammation and asthma severity.

CONCLUSIONS

Combined omics analyses provide a system biology view of complex diseases such as asthma. Table 1 shows some relevant omic biomarkers and their role in asthma. In the next years integration of omics and non-omics data has the potential of

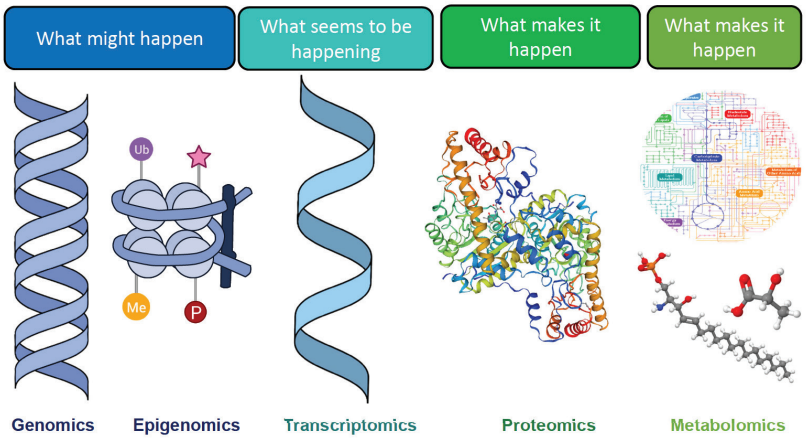

Figure 1 **Omic sciences and their aim.**

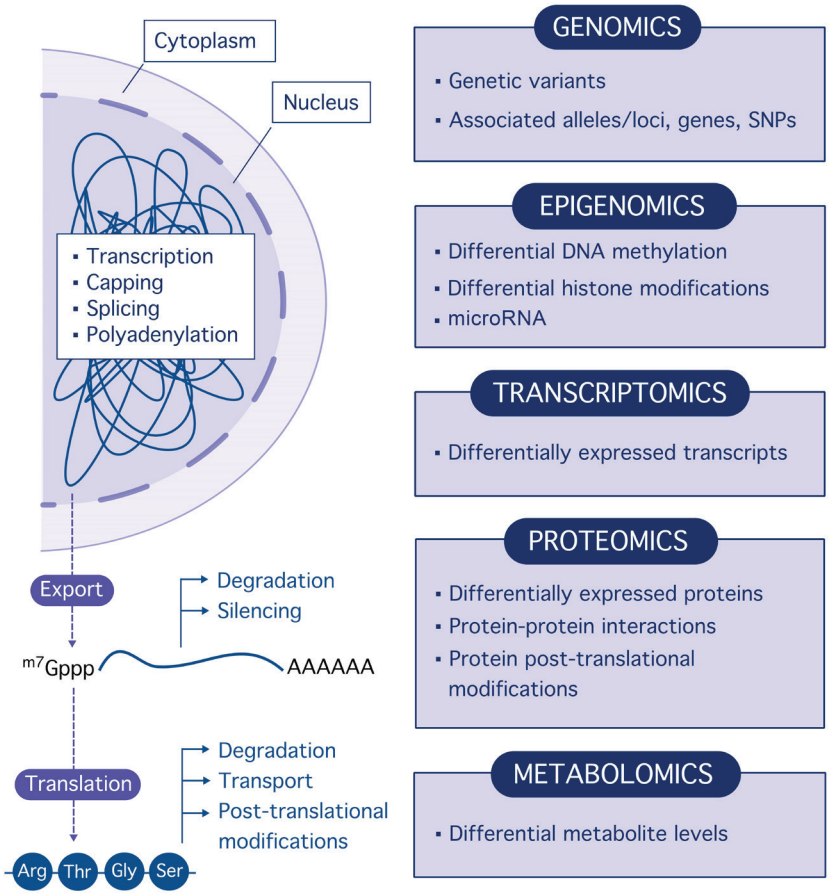

Figure 2 **Gene expression and the type of information that can be obtained on its regulation in the different omics disciplines.**

TABLE 1

Omics biomarkers in asthma

Omic science	Biomarkers/biological pathways	Description	Reference
Genomics	17q12-21 (GRB7, IKZF3, ZPBP2, GSDMB, ORMDL3, GSDMA)	Chilhood-onset asthma	Abdel-Aziz et al (2020)
	2q12 (IL18R1, IL1RL1, IL1RL2)	IL1RL1 encodes the receptor for IL33 (proinflammatory danger signal expressed in damaged airway epithelium)	Willis-Owen et al (2018)
Epigenomics	PDE6A, METTL1, CES4A, GJA4, SPP2, CDHR3, GRK5, FBXL7, LINC00704, ANKRD31, C22orf31, SUCNR1, NTRK1, PLEC, PCSK6, CAPN14, SYNPO, TSHR, NCF2, PCSK6, NUP98, BANF2, EFNA5, C15orf54, LRRFIP1, ZPLD1, CDH26, CUOX1, ADCK1, C15orf54	Top 30 EWAS linked to atopic asthma	Forno et al. (2019)
	LDLRAD3, ATXN7L1, METTL1, LINC00703, PCSK6, CDC45, LOC152225, C15orf54, CUOX1, EPPK1	Top 10 DMRs linked to allergic asthma	Yang et al. (2017)
	EPX, SORCS2, TREM2, FAM168A, SBNO2, ACOT7, LINC01140, RASSF2, GABBR1, ZBTB48, RGS3, COL15A1	Top 12 DMRs linked to allergic asthma	Cardenas et al. (2019)
Transcriptomics	Leukocyte gene signature Lung injury gene signature	Adult asthma cohort	Hekking et al. (2018)
	T-helper cell type 2 cytokines Lack of corticosteroid response	Epithelial brushings and bronchial biopsies	Kuo et al. (2017)
Proteomics	NGAL, G3P, HV320, TCO1, MYH13, LDHA, TPIS, MYH7, CFAB, AL3B1, ILEU, CLUS, LG3BP, PROL4	Sputum protein profile for Eosinophilic asthma	Schofield et al. (2019)
	LYSC	Sputum protein profile for Highly atopic asthma	
	TKT, CATA, PEDF, LG3BP, BP1B1, MUC1, CFAB, ALDOA, ZG16B, IGHG1, HEMO, A1AT, FIBG, TKT, TALDO	Sputum protein profile for Neutrophilic asthma	
Metabolomics	Sphingosine-1-phosphate	Associated with increased bronchiolitis and asthma severity	Zhu, Zhaozhong (2019)
	Nitric oxide	Increased airway inflammation Asthma severity	Kelly, Rachel (2017)

DMRs: differentially methylated regions, EWAS: epigenome-wide association studies

changing current asthma practices with a deeper understanding of the underlying mechanisms and a high impact on personalized diagnosis and intervention.

KEY REFERENCES

1. Willis-Owen SAG, Cookson WOC, Moffatt MF. The Genetics and Genomics of Asthma. *Annu Rev Genomics Hum Genet* 2018;**19**:223-246.
2. Kabesch M, Tost J. Recent findings in the genetics and epigenetics of asthma and allergy. *Semin Immunopathol* 2020;**42**:43-60.
3. Hekking PP, Loza MJ, Pavlidis S, de Meulder B, Lefaudeux D, Baribaud F, et al. Pathway discovery using transcriptomic profiles in adult-onset severe asthma. *J Allergy Clin Immunol* 2018;**141**:1280-1290.
4. Schofield JPR, Burg D, Nicholas B, Strazzeri F, Brandsma J, Staykova D, et al. Stratification of asthma phenotypes by airway proteomic signatures. *J Allergy Clin Immunol* 2019;**144**:70-82.
5. Zhu Z, Camargo CA Jr, Hasegawa K. Metabolomics in the prevention and management of asthma. *Expert Rev Respir Med* 2019;**13**:1135-1138.