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Review article

Metabolome analyses in exposome studies: Profiling methods for a vast chemical space

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ABSTRACT

Metabolic profiling (metabonomics/metabolomics) is now used routinely as a tool to provide information-rich datasets for biomarker discovery, prompting and augmenting detailed mechanistic studies. The experimental design and focus of any individual study will be reflected in the types of biomarkers that can be detected; toxicological studies will likely focus on markers of response to insult, whereas clinical case-control studies may yield diagnostic markers of disease. Population studies can make use of omics analyses, including metabonomics, to provide mechanistically-relevant markers that link environmental exposures to chronic disease endpoints. In this article, examples of how metabolic profiling has played a key role in molecular epidemiological analyses of chronic disease are presented, and how these reflect different aspects of the causal pathway. A commentary on the nature of metabolome analysis as a complex mixture problem as opposed to a coded, sequence or template problem is provided, alongside an overview of current and future analytical platforms that are being applied to meet this analytical challenge. Epidemiological studies are an important nexus for integrating various measures of the human exposome, and the ubiquity, diversity and functions of small molecule metabolites, represent an important way to link individual exposures, genetics and phenotype.

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1. Introduction

The completion of the of the human genome project promised to provide bioscientists, clinicians and epidemiologists with a new way to identify underlying genetic causes of chronic disease, estimate disease risk, conduct population/patient stratification, and identify new drug targets for therapy [1]. There are numerous examples of how candidate gene approaches, and genome-wide association studies (GWAS) have proved useful in understanding disease, and the post-genomic era has been characterized by incalculable innovation and progress [2,3]. However, it is now well recognised that the proportion of chronic disease explained by genetic variation is relatively small when compared with the influence of the environment [4–7]. Precise definitions of '*environment*' vary, but for the purposes of this commentary, it is taken to mean all non-genetic factors, which corresponds well with the concept of a human '*exposome*' as a complement to the human genome, suggested by Wild in 2005 [8–12]. The initial exposome definition that it "… *encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards*.", has been subsequently expanded and reinterpreted, but all definitions retain much of the same scope and scale [13–15]. Conceptually, the exposome is relatively simple, and has highlighted the need to devote effort to understanding environmental exposures in relation to health in addition to genomics. This approach represents a dramatic shift away from a candidate, chemical-oriented approach, to embrace the totality of exposures across different scenarios and timeframes (Fig. 1). While traditional methods for estimating exposure (e.g. personal exposure monitoring, geographic information systems) remain important in the overall exposure story, characterizing the exposome is predominantly led by the application of omics platforms that provide rich individual-level biological profiles. The blend of these techniques is clearly important to those designing studies of the exposome, and many factors play a part in determining which are used (e.g. life-course studies vs adult exposures vs mother-child studies), which has been highlighted in recent articles [16,17]. Metabolic profiling (metabonomics/metabolomics) [18,19] is central to these analyses, and several reviews provide further rationale and examples of how this is being implemented [20–23].

2. Throwing down the gauntlet: characterizing chemical and biological space

The full complement of small molecules in a given tissue, biofluid or compartment is known as the metabolome. Biological systems efficiently create complex metabolomes through the combinatorial action of multiple enzyme systems with varying substrate affinities and reaction rates. For example, a simple xenobiotic may (although not always) be metabolized to a dizzying array of phase 1 and phase 2 metabolites, with these distributed unequally at cellular, tissue and system level, and each having a unique set of interactions and responses. The human body also exists in close companionship with a wide variety of other organisms, each with their own genomes and metabolomes; the term '*superorganism*' has appropriately been used to describe the ensemble [24]. Human gut microbiota exhibit both spatial and temporal dynamics, and are intimately involved in co-metabolism across a wide range of substrates, meaning that the already complex picture of the human metabolome presented above is incomplete. The gut-host metabolic interface can give rise to diverse compound metabolism, with both potentially beneficial and adverse consequences [25]. Furthermore, the microbiotic composition is modulated by the gut environment - including its metabolic profile – meaning it is not a simple exposure, but inherently plastic and variable. There is currently much interest in understanding the role of microbiota in human health, as a potential dietary and/or therapeutic modifiable factor. Researchers have attempted to partition subsets of chemicals relevant to their own biological interest area, resulting in a variety of metabolomes being defined, echoing efforts in genomics to sequence species/individual genomes. These include the human blood and urine metabolomes [26,27], and those relating to nutrition [28], herbs [29], and pharmaceuticals, supplements, cosmetics, toxins, and substances of abuse [30–32].

2.1. Chemical space

The chemical space in which these processes occur is vast. Estimates of how vast vary considerably, but many estimates from the pharmaceutical industry put the number of chemicals that might have drug-like (i.e. potentially biologically active) properties at around 10^{60}, and dwarfs the current list of human-synthesized compounds (listed in the Beilstein database) [33–36]. The authors of these papers comment that ennumeration of all compounds is nether helpful nor possible – the search space is so large – but focused libraries of compounds help cover the chemical space efficiently. In a similar way, while any of these compounds has the potential to exist – they could be synthesised given sufficient effort - most are irrelevant in terms of a real exposure that has a meaningful effect on the metabolome, and consequently the health status of an individual. The use of analytical methods that are sufficient broad so as to help cover the potential exposure/metabolome space are likely to be most useful. Interestingly, not only is the chemical space vast, but so to is the range of concentrations experienced, both inside and outside of the body. Rappaport et al. (2014) compiled the available, published literature values for 1500 chemicals observed in human serum or plasma samples. These compounds included dietary components, drugs, and environmental pollutants – and revealed these span 11 orders of magnitude. Interestingly, these authors demonstrated that environmental pollutants were present at much lower levels (typically 10–1000-fold) than those of other sources, which were comparable in magnitude [37]. If we are to attempt to dissect exposures from various sources, and the responses that are elicited by their ensemble action across the vast physicochemical and concentration ranges, then appropriate, high-capacity methods for interrogating biofluids are needed.

2.2. Codes

As described above, the human metabolome is a complex, responsive, dynamic part of the exposome, with comparable complexity to that of the human genome. However, the

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