Chapter 1

The Exposome Paradigm in Environmental Health

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ABSTRACT

Connectivity introduces a new exposome based paradigm in environmental health. This denotes an approach that builds on the exploration of the interconnections between the co-existence of multiple exogenous and endogenous stressors and the different scales of biological organization. Coupling the two results in the final adverse health effect. This differs from the conventional paradigm, which seeks to shed light on the identification of singular cause-effect relationships between stressors and health outcomes. It creates a new way of combining health-relevant information coming from different disciplines, treating all factors affecting internal and external exposome are as covariates. Their functional integration into results in understanding the complex interaction between genome and exposome. The applicability of the exposome (and more specifically the connectivity) approach towards a better understanding of the exposure, sociodemographic and biological factors interplay in the association between environment and disease, is demonstrated in two different case studies.

INTRODUCTION

The exposome (Wild, 2005) refers to all the exposures – exogenous and endogenous - throughout a person's life starting from conception, and it simultaneously identifies, characterizes and quantifies them along with modifiable risk factors in order to understand the person's predisposition to diseases.

The human genome preceded the exposome. Decoding the human genome (Schmutz et al., 2004) significantly contributed to a deeper understanding of the underlying causes of disease. However, its explanatory power regarding the health burden of the population is limited, as environmental factors are equally or eventually more important than genetic characteristics.

What is actually critical is the interaction of environmental factors with biological systems. Towards a better understanding of the causal links among the genome, the environment and human disease,

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unraveling the exposome implies that both environmental exposures and genetic variation are reliably measured simultaneously (Sarigiannis et al., 2019a).

Given the enormous amount of information that needs to be integrated, unraveling the exposome is daunting. Various efforts have taken place (e.g. COPHES (harmonization of HBM), EHES (harmonization of Health Surveys), EU-menu (harmonization of data collection on food consumption), CHICOS (harmonization of child cohort studies) or U-BIOPRED (unbiased biomarkers in prediction of respiratory disease outcomes)) aiming to harmonise existing, often disparate information. At the moment, the largest exposome ongoing project is HEALS; HEALS employees a large array of technologies for both external (Asimina et al., 2018; Loh et al., 2017b) and internal (Sarigiannis et al., 2016) exposome, that involve multiple sensors for monitoring exposure, biomonitoring analysis, physiology based biokinetic modelling, multi-omics and advanced bioinformatics and advanced statistics for environment health associations, that support the efficient design and execution of large-scale exposome studies. The other two key projects that comprised the EU exposome initiative, include Exposomics (led by Imperial College, in London, UK) and HELIX (led by CREAL in Barcelona, Spain). In Exposomics, a personal exposure monitoring system that involved sensors, smartphones, geo-referencing and remote sensing has been developed for constructing external exposome, followed by biological samples analysis. The aim was to identify associations between external exposure and molecular fingerprints (through omics analysis) of cancer (Chadeau-Hyam et al., 2013; Vineis et al., 2013; Vineis and Wild, 2014). On the other hand, the Human Early-Life Exposome (HELIX) project (Vrijheid et al., 2014) aims at the association of early-life cumulative exposure with omics and child health outcomes. Finally, CROME (Cross-Mediterranean Environment and Health Network) is a fourth exposome EU project, with a particular focus on environmental health issues of Mediterranean countries. CROME paid particular attention on integrating human biomonitoring for developing individual exposome, highlighting associations among environmental, dietary and genetic factors with adverse health outcomes such as child neurodevelopment (Snoj Tratnik et al., 2017) and cancer (Sarigiannis et al., 2015b), paying a particular attention to toxicokinetics (Andra et al., 2015; Sarigiannis et al., 2016; Sarigiannis et al., 2019b).

The two key exposome-related initiatives in USA were funded by NIEHS, including the HERCULES center at Emory University in Georgia and the Exposome Research Center at the University of California at Berkeley. The approach of HERCULES is based on a multi-faceted approach to the exposome (Miller, 2014), aiming at the estimation of allostatic load related to environmental factors over individual lifetime (Miller and Jones, 2014; Niedzwiecki and Miller, 2017). The UC Berkeley Center has a different approach, paying more attention on exploiting untargeted metabolomics (Rappaport et al., 2014) for developing individual exposome profiles for identifying the associations among environmental factors and adverse health effects (Rappaport, 2018), employing a top-down approach (Rappaport and Smith, 2010).

The progressive digestion of the exposome concept by the scientific community, impacted significantly the domain of environmental health. Firstly, it was very important that additional information than typical exposure biomarkers can be retrieved from biomonitoring, serving the needs for an exposome approach (Dennis et al., 2017). A key component of exposome studies is that they include the full picture of stressors that are relevant for health, coming from both endogenous and/or exogenous sources. The full array of human biosample analysis that involves exposure biomarker analysis and multi-omics (transcriptomics, proteomics, metabolomics, adductomics and epigenomics), results in the generation of big data that has to be put into a plausible biological context through appropriate computational tools (Manrai et al., 2017); these include both the ones aiming at elucidating the link of both external-internal

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