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The role of low-grade inflammation and metabolic flexibility in aging and nutritional modulation thereof: A systems biology approach☆

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ABSTRACT

Aging is a biological process characterized by the progressive functional decline of many interrelated physiological systems. In particular, aging is associated with the development of a systemic state of low-grade chronic inflammation (inflammaging), and with progressive deterioration of metabolic function. Systems biology has helped in identifying the mediators and pathways involved in these phenomena, mainly through the application of high-throughput screening methods, valued for their molecular comprehensiveness. Nevertheless, inflammation and metabolic regulation are dynamical processes whose behavior must be understood at multiple levels of biological organization (molecular, cellular, organ, and system levels) and on multiple time scales. Mathematical modeling of such behavior, with incorporation of mechanistic knowledge on interactions between inflammatory and metabolic mediators, may help in devising nutritional interventions capable of preventing, or ameliorating, the age-associated functional decline of the corresponding systems.

1. Introduction

Aging is a biological process characterized by the progressive functional decline of many interrelated physiological systems, at multiple levels of biological organization: molecular, cellular, tissue or organ, and systems level. In particular, inflammation is strongly affected by the aging process. Elderly people often present mildly elevated blood levels of inflammatory mediators, and the slow development of this state of low-grade, chronic, systemic inflammation with age has been termed "inflammaging" (Cevenini et al., 2013; Franceschi et al., 2007, 2000). Some of these mediators have been identified as risk factors for age-associated diseases, such as arthritis, sarcopenia, cardiovascular diseases, type II diabetes, neurodegeneration, many cancers, etc. (Blagosklonny and Hall, 2009), and suggested to provide the "common soil" for development of these diseases (Salvioli et al., 2013). Low-grade inflammation can be driven by metabolic dysfunction brought about, for instance, by overnutrition, in which case it has been referred to as "metaflammation" (Gregor and Hotamisligil, 2011). Metaflammation includes infiltration of immune cells in metabolic organs, caused by reaching the expandability limits of these organs. In addition, both aging and age-related diseases may lead to loss of "metabolic flexibility", that is, loss of the ability of cells and tissues to adapt fuel utilization to fuel availability (Storlien et al., 2004). Lifestyle interventions based on a balanced diet and adequate amount of physical activity are one of the most successful strategies for restoring metabolic health (Biagi et al., 2012; Jeffery and O'Toole, 2013). Therefore, nutritional interventions may be successful in controlling low-grade inflammation and improving metabolic flexibility in elderly people.

Though nutrition is a modulator of both aging and metabolic function, the mechanisms of this modulation are not entirely understood and most likely depend on a complex interplay of effects of macro- and micro-nutrients. Still, it would be most helpful to be able to devise nutritional strategies with predictable health effects in the elderly, taking into account known personal

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susceptibilities, as well as current health status. Considering the importance of inflammation in the aging process, inflammatory biomarkers, possibly in combination with more specific indicators of metabolic function, can be used as a proxy of health status and guide the implementation of such strategies.

An important challenge in this endeavor is the fact that inflammatory mediators are plentiful and heavily intertwined, forming a complex web of sensors, mediators and effectors for the inflammatory response, characterized by a high level of redundancy and pleiotropy. Such complexity requires that inflammation be understood and studied as a system of interacting components, rather than as a collection of various molecules, each having its own specific role. Systems biology offers an ideal framework to accomplish such a task, both in terms of identifying meaningful components and interactions, as well as in representing, analyzing, and predicting the behavior of the whole system, also through development of mathematical and computational models.

The aim of this review is to discuss how systems biology can help in clarifying and quantifying, on one hand, the relationships between low-grade inflammation, aging and metabolic flexibility, and on the other, the impact of nutrition on inflammatory and metabolic parameters. The models described in this review will be the basis of the systems biology analyses to be performed in the framework of the European project NU-AGE. The aim of NU-AGE is to counteract inflammaging through a whole diet approach and to acquire measures of putative biomarkers that could be modulated by diet using omics techniques (for details see the paper from Santoro et al., 2014). In the next section we summarize what systems biology is and how it can help in tackling this problem. The following sections will discuss specific examples of systems biology approaches (mainly focusing on modeling strategies) to the understanding of low-grade inflammation and metabolic flexibility in the context of aging.

2. Systems biology approaches

Systems biology arose as a scientific field in the early 21st century, propelled by technological advances in both experimental measurement techniques and available computational power. These advances allowed scientists to probe biological processes at the molecular scale in a high-throughput fashion (see Box 1), as well as store and quantitatively analyze the resulting data, nowadays collectively referred to as omics data (Hawkins et al., 2010; Mallick and Kuster, 2010; Portela and Esteller, 2010; Vinayavekhin et al., 2010). The most common types of omics data are genomics (analysis of the genome, including epigenetic modifications), transcriptomics (analysis of RNA levels), proteomics (analysis of protein levels), and metabolomics (characterization of metabolite abundance). Omics data can be captured at the single-cell level (Zong et al., 2012), from body fluids or sets of circulating blood cells, or at tissue or organ level. The key advantage of such high-throughput screening is its molecular comprehensiveness, which provides a rich molecular portrait of the system, enabling scientific discovery, supplying a large molecular base for comparisons between experimental conditions (e.g. healthy and pathological states), and all in all providing scientists with ample hypotheses for future research. Recent reviews, by Gardy et al. (2009) and Afacan et al. (2012), discuss the insights gained from the application of omics technologies in the fields of innate immunity and nutritional immunology, respectively, as well as important challenges in such applications.

While it is true that high-throughput methods have allowed for a more comprehensive description of biological phenomena than ever before, interpretation of the vast amounts of data generated in a given experiment is almost never straightforward. On one hand, technology-related issues, such as a low signal-to-noise ratio or the limited dynamic range of available platforms (especially in proteomics), require extensive pre-processing of raw data; on the other, the large number of probed molecules make data analysis a challenging procedure, the conclusions of which hinge on proper control of false positives rates and follow-up validation

Box 1. Data resources

The need to store the massive amounts of data produced by high-throughput technologies boosted the development of ad-hoc designed databases, giving to almost each omics field one or more reference data banks. Some of these databases are geared toward keeping comprehensive and quality-controlled information on each known molecule or gene, while others focus on archiving and disseminating results from experimental studies using omics technologies. In the field of genomics, ENSEMBL (Flicek et al., 2012) and dbSNP (Sherry et al., 2001) are the main sources of curated information, whereas ArrayExpress (Helen Parkinson et al., 2009) and GEO (Barrett et al., 2013) work as repositories of transcriptomics datasets. UniprotKB (The Uniprot Consortium, 2012) is the most comprehensive resource of manually annotated protein information, whereas publicly available datasets of proteomics studies may be found in the PRIDE database (Vizcaíno et al., 2013). For metabolomics, the HMDB database (Wishart et al., 2009) contains detailed information on more than 40,000 human metabolites and small molecules, whereas metabolomics datasets may be found in MetaboLights (Haug et al., 2013). Biochemical pathway databases such as KEGG (Kanehisa et al., 2012) and REACTOME (Matthews et al., 2009) may be used to explore the biological context and functional roles of these molecules. Along with these generalist databases, other much more focused resources have been developed to serve the immunology community (reviewed in (Gardy et al., 2009)). InnateDB (Breuer et al., 2013), for instance, groups together information on mediators of the innate immune response in different mammalian organisms (human, mouse, bovine), providing manually curated data on immune-related genes, proteins, and interactions. In addition, the nutritional community has joined to develop the nutritional phenotype database (dbNP), which stores different types of omics data (transcriptomics, metabolomics, proteomics, etc.) and corresponding metadata from studies with a complex experimental design (e.g. crossover) (Van Ommen et al., 2010). This database is being used in the NU-AGE project to store all data of the human intervention. Effective sharing of data amongst the scientific community critically depends on standardization of formats, languages, and annotation requirements, for which XML-based encodings have been widely adopted. Strict guidelines describing the ''minimum required information'' for different kinds of studies have been proposed, e.g. MIAME or MINSEQE for microarray and high-throughput sequencing (Brazma, 2009; Brazma et al., 2001), or MIAPE (Taylor et al., 2007) for proteomics. These guidelines strongly emphasize the requirement of metadata (''data about the data''), in order to ensure replicability and proper interpretation of the results. In general, annotation of omics datasets relies on biomedical ontologies (e.g. Gene Ontology, for describing genes and gene products), which establish a formal and structured representation of biomedical knowledge, facilitating automated querying. The BioPortal website (http://bioportal.bioontology.org/ontologies) provides a listing of commonly used biomedical ontologies, as well as tools for searching and comparing terms across different ontologies.

Databases hosting massive quantity of information must go hand in hand with the development of easy and scalable querying methods. Raw data FTP access is usually granted to users requesting large datasets, whereas focused requests can be managed via Web-based interfaces in each database (e.g. the ENSEMBL genome browser), or application programming interfaces (APIs) relying on REST or SOAP protocols.