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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.

studies. Most commonly, exploratory data analyses, such as principal component analysis (PCA), are first employed for purposes of dimensionality reduction, whereby the original variables are recombined into fewer, more meaningful and uncorrelated variables. A complementary class of approaches are the ones based on representation of the data as a network, where each node represents a measured variable (e.g. a protein or transcript) and an edge between two nodes represents a relation between variables, derived from either experimental data or prior biological knowledge (Remondini and Castellani, 2011). These relations may be quantitative or qualitative: quantitative relations include, for example, a stoichiometric relation (of an enzymatic reaction), or the correlation between two variables, measured in a time series; qualitative relations include possible or known physical interactions between variables (Frankenstein et al., 2006). Besides aiding researchers in the visualization and visual exploration of high-dimensional data, analysis of a network's structural properties can reveal the relevance of each node in the network, allowing for inferences about the effects of node deletion on network integrity to be made. The network approach gained momentum in the last few years, as it shifted the emphasis from single components to relations between components, and from traditional reductionist approaches to a more holistic perspective of the system. However, while focusing on interactions between system components, network analyses usually fall short of elucidating system behavior, which depends on more than just the structural properties of the network (Cowan et al., 2012; Lima-Mendez and van Helden, 2009; Zhou and Nakhleh, 2011).

Indeed, the dynamics of actual mechanistic interactions between system components are essential for understanding – as well as reliably predicting – system behavior (Alexander et al., 2009). Analysis of such dynamics can be accomplished via mathematical modeling, where the system is characterized by its state and a temporal evolution rule. The state of the system at a certain moment in time is defined by the numerical value (e.g. concentration, number of molecules) of each component at that moment, and the evolution rule dictates how changes in each system component quantitatively depend on other system components. The most widely used formalism for representing dynamic systems are ordinary differential equations (ODEs), but other representations may be more appropriate in specific contexts. In particular, when a continuous approximation of the system is not possible, due, for example, to low numbers of participating molecules, formalisms such as the master equation, agent-based models or Boolean networks may be used; additionally, when one is interested in studying the variability in system behavior due to stochastic effects, appropriate approaches include stochastic differential equations, the Fokker–Planck equation, or the master equation (Van Kampen, 1981). In order for dynamical modeling to be feasible, mechanistic information regarding relevant interactions (e.g. ligand–receptor association constants) must be available. Most often, however, this is not known for all interactions in a system, and empirical or approximate relations may need to be used instead. Depending on the goal of the modeling, it may be appropriate to represent in great mechanistic detail a certain portion of the system – to study, for example, the impact of pathological dysregulations that translate to changes in the associated mechanistic parameters – whereas other portions of the system could be "black-boxed", that is, described by laws that do not represent actual mechanisms but that do agree with empirical observations (see Fig. 1). Furthermore, modeling of a given biological phenomenon may require consideration of dynamics at very disparate scales, both in time (e.g. the seconds of biochemical reactions versus the weeks needed for clearing an infection) and space (the detection of a pathogen by a single cell versus the system-wide changes in metabolism caused by the infection). Models at different scales may be built using different formalisms and used to answer specific questions (e.g. how a mutation affects the probability of an interaction), while linking of such models – referred to as multiscale modeling – should provide insights on emerging properties, and is one of the frontiers of system biology

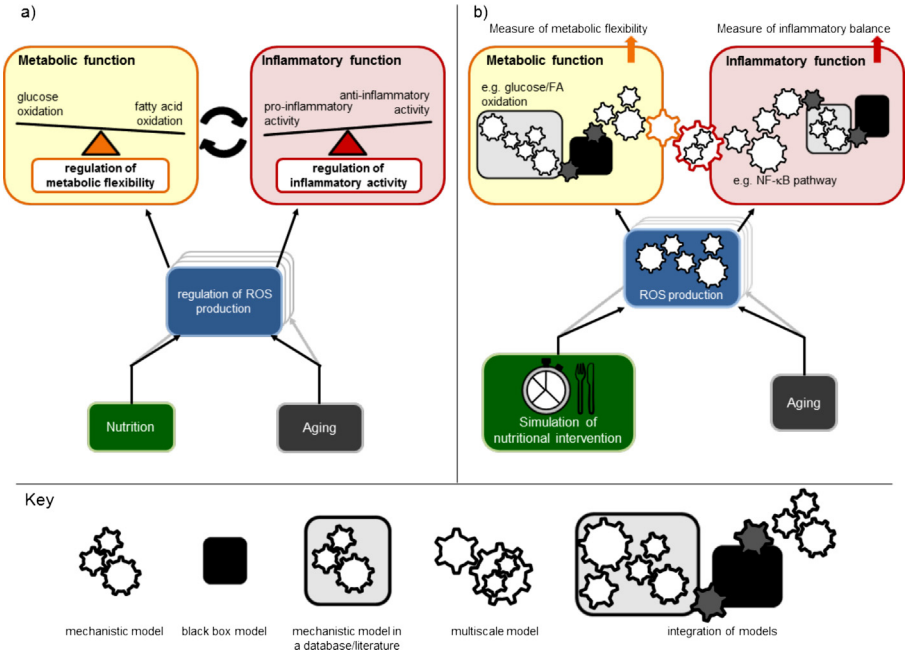

Fig. 1. Diagram showing simplified biological relations (a) and methodological aspects (b) in the study of the modulation of metabolic flexibility and inflammation by nutrition and aging. (a) Both nutrition and aging modulate metabolic and inflammatory function in humans, ROS production being one of the possible mechanisms by which this modulation takes place. Dysregulated ROS production may lead to a loss of metabolic flexibility, as well as local and systemic imbalances in inflammatory mediators. (b) Mathematical modeling can help in the study of the biological mechanisms involved in these processes, and integration of different types of models, along with in silico simulation of nutritional interventions, may help in probing the contribution of each mechanism to this modulation and in obtaining or interpreting measures of metabolic flexibility and inflammatory imbalance.

(Alberghina and Westerhoff, 2005; De Graaf et al., 2009). Inflammation is a biological system that requires systems biological methods to fully understand the temporal and spatial complexity of the responses to all kinds of stressors.

3. Modeling low-grade inflammation in aging

Low-grade, chronic, systemic inflammation, may be defined as a 2- to 3-fold elevation of circulating inflammatory mediators (Krabbe et al., 2005; Petersen and Pedersen, 2005), usually associated with the innate arm of the immune system. It is a state that develops slowly (in contrast to pathological acute inflammatory responses leading, e.g. to sepsis), and its origin cannot be easily identified (in contrast to chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, where additional symptoms identify local dysregulated inflammation). This makes it difficult to develop appropriate therapeutic strategies that target both cause and symptom (inflammation) in a concerted fashion.

In elderly people, the development of this state of low-grade inflammation has been termed inflammaging (Franceschi et al., 2007; Licastro et al., 2005), and several studies (though not all) have identified associations of increased levels of inflammatory markers with increasing age, frailty, cardiovascular disease, or mortality in older persons (Alvarez-Rodríguez et al., 2012; Forsey et al., 2003; Fulop et al., 2010; Wikby et al., 2006). These associations are seen in various biomarkers (Singh and Newman, 2011), the most prominent of which are the cytokines interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF); their soluble receptors IL-1 receptor antagonist (IL-1Ra), TNF receptor (TNF-R) and soluble IL-6 receptor (sIL-6R); the acute phase protein C-reactive protein (CRP); and total leukocyte count. In centenarians (people older than 100 years), anti-inflammatory markers, such as IL-10, have been suggested to play a role in protecting individuals from an otherwise pro-inflammatory profile (Sansoni et al., 2008). Though it has been suggested that cytomegalovirus infection could be a major driver of inflammaging, the evidence for this is conflicting (Bartlett et al., 2012; Vescovini et al., 2007, 2010).

As an intracellular integrator and regulator of many of the extracellular signals of inflammation, the NF-κB transcription factor, along with the members of its signaling pathway (the NF-κB system), are thought to play a major causative role in inflammaging (Chung et al., 2002; Csiszar et al., 2008; Salminen et al., 2012, 2008). The NF-κB system is composed of a large set of proteins that regulate inflammatory responses to numerous stimuli (Pahl, 1999), including bacterial products, such as LPS, inflammatory cytokines, such as IL-1 and TNF (Osborn et al., 1989), and oxidative stress. Given its prominent involvement in human pathology, the NF-κB system has been the subject of much experimental study in molecular and cellular biology. These studies have resulted in an extensive knowledge of the system components and mechanisms of signal transduction. Activation of the NF-κB system results in transcription of over 150 target genes, with subsequent production of inflammatory mediators such as cytokines, chemokines, and cell adhesion molecules. Such activation is controlled by three IκB isoforms (IκBα, -β, and -ε), which are constitutively bound to NF-κB, preventing association with its target genes in the nucleus. Activation signals cause the IκB kinase (IKK) complex to phosphorylate the IκB isoforms, which are then readily degraded (Ghosh et al., 1998), allowing NF-κB to translocate to the nucleus and bind DNA. While network analyses of the NF-κB interactome (Tieri et al., 2012) have provided a comprehensive view of the parts involved, further efforts must be geared toward the quantitative study of the dynamical behavior that such functional relations impart to the system, as this will prove crucial for the development of successful therapeutic strategies.

In this regard, mathematical modeling of NF-κB system dynamics has played an essential role, both guiding experimental strategies and highly benefiting from the wealth of experimental data available (Basak et al., 2012). As Basak et al. (2012) point out, their concerted experimental and theoretical efforts were initially undertaken with the purpose of disentangling the differential roles of the different IκB isoforms in producing the observed temporal activity profile of NF-κB in response to inflammatory stimuli, as suggested by biochemical time-course studies. Accordingly, they enabled the quantitative analysis of known and hypothetical compensation mechanisms among IκB isoforms, and contributed to the identification of a late-acting isoform (IκBε), critical for dampening IκBα-mediated oscillations during long-lasting NF-κB activity. However, such a concerted approach has generated insights well beyond the scope of its initial purpose. Model development itself resulted in revision of literature data regarding degradation rates of bound and free pools of different IκB proteins, whereas computational sensitivity analyses revealed that the distinct degradation rates of these pools constitute a cross-regulation mechanism contributing to the robustness of the system response (O'Dea et al., 2007). Mathematical modeling also suggested that, besides its main function as a transducer of extracellular signals, the NF-κB system may have the ability to integrate intracellular available metabolic information into its response, due to the high IκB protein synthesis required at steady-state to counteract the proteins' instability. Such integration of metabolism and inflammation is now the subject of ongoing studies (Tornatore et al., 2012). When new experimental data showed that the IκBδ isoform had a long half-life, as compared to the usual timeframe of NF-κB activity, incorporation of this information into the model allowed for quantitative assessment of the effects of prior inflammatory stimulation on the responsiveness of the system (i.e. assessment of pre-conditioning effects). It was found that high IκBδ abundance could have tolerizing effects on inflammatory signaling, allowing IκBδ to function as an integrator of cellular exposure history to inflammatory stimuli, and a potential target for cross-talk mechanisms with other developmental functions of NF-κB signaling.

Although the NF-κB system is a central signaling pathway in inflammation, it is certainly not the only one, and several other intra- and inter-cellular communication pathways are of relevance for the study of inflammation. Nevertheless, one key aspect that comes out of the dynamic modeling approach, and that may be generalized to the study of any system, is that, in addition to the molecular identity and amplitude of the stimulatory signal, its temporal characteristics, such as duration or frequency of stimulation, also play an important role in determining cellular behavior (Ashall et al., 2009; Behar and Hoffmann, 2010). In the context of intercellular communication – autocrine and paracrine signaling – the rate of depletion of cellular receptors in stimulated versus unstimulated conditions, for example, has been found to play a major role in determining transient versus persistent responses to the TGF-β family of ligands (Vilar et al., 2006; Zi et al., 2011). Cytokines and cytokine families have a prominent role in the coordination of inflammatory responses, their action often depending on a host of agonist or antagonist soluble receptors, as well as on the simultaneous presence of different receptors at the cell surface. IL-6, for example, belongs to the IL-6 family of cytokines, which share the common gp130 signaling unit, and is a cytokine with pleiotropic effects, thought to have both pro- and anti-inflammatory (or regenerative) properties (Scheller et al., 2011b). IL-6 signaling requires two types of receptors to be present at the cell surface: a cognate receptor (gp80), with high specificity for this cytokine, and the signaling receptor gp130. These receptors are found in soluble form in plasma, and at the cell surface, with gp130 widely distributed and gp80 expressed

mostly in hepatocytes and immune cells (Garbers et al., 2012). Thus, IL-6 may signal directly, in cells that express both types of receptors, or indirectly, in cells that only express gp130, by first binding the soluble version of gp80 (Rose-John, 2012). This interplay between soluble and membrane-bound forms of the receptors may result in a multiphasic IL-6 signal, which is thought to be involved in the switch from neutrophil to macrophage infiltration in local inflammatory processes (Scheller et al., 2011a,b). Therefore, dynamical models of inter-cellular IL-6 signaling may help in understanding the coordination, and possible mechanisms of dysregulation, of the inflammatory response. They could be used, for example, to quantify the relative effects of broken feedback mechanisms versus genetically determined overproduction of IL-6, in the overall outcome or temporal profile of an inflammatory response. Again, building this type of models requires information on molecular interactions properties, such as physico-chemical association constants (to both soluble and cellular receptors), measurements of the distribution of both receptors on different cell types, and data on the rates of receptor degradation and translocation to the cell membrane. Additionally, data regarding cytokines that are known to stimulate or be stimulated or inhibited by IL-6, on the same time scale as the previous phenomena, may also be necessary. In other words, the knowledge required for model building comes, in this case, from heterogeneous experimental sources (e.g. binding assays, fluorescence microscopy, flow cytometry), as it characterizes heterogeneous interactions between various system components (see Box 2). This knowledge is, in part, available in the literature, and further experiments could help in validating specific hypotheses regarding the missing information.

Combination of inter- and intracellular signaling models could also prove useful in understanding the influence of signaling molecules on cellular phenotypes, e.g. M1 and M2 macrophages, or Th1, Th2, and Th17 T-cells (Busse et al., 2010; Hong et al., 2011; Mendoza and Pardo, 2010; Santoni et al., 2008), which are usually defined by a specific set and relative amounts of secreted mediators, as well as by the set of mediators promoting their differentiation. In this context, single-cell experimental techniques may prove useful in refining cellular phenotype classification, by determining, e.g. if cytokine production by different phenotypes occurs in a sequential or simultaneous manner (Han et al., 2012). Joint experimental and mathematical analysis of the relations between different cellular phenotypes and cell surface distributions of cytokine receptors is important because the levels of the corresponding soluble ligands (and any associated agonists or antagonists) might be tightly adjusted to both, and thus impact their behavior. Such adjustment could be crucial for the production of a self-limited, healthy inflammatory response, and dysregulations in overall soluble environment could be conducive to imbalances in levels of cell surface markers (Valeyev et al., 2010).

It is important to bear in mind that functional motifs (Fu et al., 2012) may be found at multiple biological levels – intracellular transcriptional pathways, interactions between soluble ligands and their receptors or circulating ligands and cell surface receptors – acting in a coordinated fashion in the interest of homeostatic balance (Chizzolini et al., 2009). It is almost certain that similar functional patterns will be found at these different levels, with different biological parameters proving critical in each level (Fowler et al., 2012; Rivière et al., 2009). Integration of such interrelated modules, followed by in silico hypothesis testing, could help in determining, for example, the comparative dominance, redundancy, robustness, or degree of interdependence of different signaling pathways, in revealing the most effective therapeutic targets at different time windows (Clermont et al., 2010), and also in directing further model development, by providing criteria for model refinement (Dittrich et al., 2012) or abstraction, in conjunction with modeling goals. Thus, deposition of models in public repositories – in such a way that they can be coupled together and simulated – is a crucial requirement for their usefulness and translational power (Vodovotz et al., 2008) (see Box 2).

Box 2. Model resources

For quantitative models of biological processes, the BioModels and CellML databases are the main available resources. The BioModels database (Li et al., 2010) currently hosts 142,973 models, the majority of which generated by overlaying qualitative pathway information with kinetic rate constants from other databases, in the context of the Path2Models project. The remainder of the models belong to either the curated (436) or non-curated (488) branch of the database (as of May 1st 2013). Similarly, the CellML Project database (Yu et al., 2011) contains over 500 curated quantitative models, including models of respiratory and cardiovascular physiology, biomechanics and pharmacology, in addition to the molecular scale models typically found in BioModels. Quantitative models are most commonly specified in the SBML (Hucka et al., 2003) standard, with the minimum required information set by the MIRIAM guidelines and model annotation relying on the SBO ontology (Le Novère, 2006).
Parameters in quantitative models must be either estimated from the experiments associated with development of the model, or gathered from the existing literature or databases. In particular, for models of inflammatory signaling, protein interaction data (e.g. dissociation constants) may be especially relevant. These may be found, among many others, in the BIND (Bader et al., 2003) or IntAct (Kerrien et al., 2012) databases, which can be jointly queried using the APID or PSICQUIC tools (Aranda et al., 2011; Prieto and De Las Rivas, 2006). For enzymatic reactions, the SABIO-RK (Wittig et al., 2012) and BRENDA (Schomburg et al., 2013) databases contain extensive quantitative information on thousands of kinetic parameters (e.g. velocity and half-saturation constants). Though these are valuable resources, kinetic rates obtained from biochemical assays may only be a rough estimate of in vivo kinetics, and have not usually been collected for all the reactions considered in a model (Van Eunen et al., 2010, 2012). In addition to biochemical kinetics data, quantitative models may need specification of parameters such as typical cell or protein sizes, half-lives, diffusion constants, or other biophysical properties. In this context, the BioNumbers database, containing ''key numbers in molecular and cell biology'' (Milo et al., 2010), is a most valuable resource, as manual search for these properties is notably time-consuming. In earlier stages of model building, more qualitative databases and ''meta-databases'' of known and predicted protein–protein interactions, such as the STRING database (Szklarczyk et al., 2011), may also be helpful in exploring and identifying potential model components.
As with model definition, sharing of results from model analysis and simulation also benefits from the use of standardized formats and ontologies (e.g. the SED-ML and SBRML standards for describing simulation specifications and results, respectively, and the KiSAO and TEDDY ontologies for annotation purposes), while model building and simulation may be done online, using platforms such as JWS Online/OneStop (Olivier and Snoep, 2004) and VCell (Loew and Schaff, 2001). While each individual model is aimed at understanding a specific biological phenomenon, integration of multiple models could help define a wider biological question and provide useful insights into the behavior of the corresponding system. Model interoperability is critical for this type of multiscale modeling (Bassingthwaighte and Chizeck, 2008), especially when the scales of the component models are heterogeneous (e.g. molecules, physiological electrical signals), and is a central concern in the ongoing development of simulation platforms (Beard et al., 2012).

4. Modeling metabolic flexibility in aging

Besides inflammation, another important function thought to be compromised in the elderly is metabolic flexibility (DiPietro, 2010). Metabolic flexibility is the ability of cells and tissues to switch from a state of predominant lipid oxidation and high rates of fatty acid uptake, during fasting conditions, to the suppression of lipid oxidation and increased glucose uptake, oxidation, and storage, under insulin-stimulated conditions or after a meal (Galgani et al., 2008). Following a meal, during the postprandial phase, blood concentrations of nutrients are high and pancreatic β-cells respond by releasing insulin into the bloodstream. In myocytes, the pivot for glucose and fatty acid oxidation, insulin receptors bind insulin, which results in translocation of glucose receptors to the plasma membrane, allowing glucose to enter the cell. The rise of nutrients inside the cell leads to increased levels of citrate in the mitochondria, which is then displaced to the cytosol, where it stimulates lipogenesis and inhibits fatty acid oxidation. Metabolism is consequently shifted toward oxidation of glucose and storage of fatty acids. During the fasting phase, plasma glucose and insulin drop, whereas plasma concentration of free fatty acids coming from adipocytes rises. The energy demand causes a drop in citrate levels, which results in a shift of metabolism toward oxidation of fatty acids.

Both overnutrition and differential macronutrient imbalances may lead to impairment of metabolic flexibility in several ways. First of all, excess glucose inside the cell results in production of reactive oxygen species (ROS) and oxidative stress. The ROS produced lead (among many other effects) to intracellular signals that stimulate inflammation and inhibit insulin signaling – such as protein kinase C (PKC), c-Jun-N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK). In particular, the JNK stress pathway performs this inhibition by activating FOXOs. In addition, FOXOs inhibit leptin-induced appetite suppression in the hypothalamus, impair insulin-induced β-cell proliferation in the pancreas, and affect mitochondrial biogenesis, which should act against ROS (Nunn et al., 2009; Ponugoti et al., 2012). Secondly, overnutrition results in an inability of adipose tissue to deal with excess lipids, leading to lipid accumulation in ectopic tissues. Eventually, this accumulation can induce lipotoxicity, as reflected by the cellular accumulation of long chain fatty acyl-CoA (FA-CoA), diacylglycerol (DAG), triacylglycerol (TAG) and ceramide. These lipid species, along with inflammatory cytokines released by adipose tissue (e.g. TNF-α), ultimately impair insulin signaling, by increasing serine phosphorylation of the insulin receptor and reducing the activation of PKB/Akt (Galgani et al., 2008). Finally, inhibition of insulin signaling due to overnutrition leads to impaired translocation of GLUT4 during a meal, resulting in an inability of the cell to shift toward glucose oxidation; conversely, during the fasting phase, hyperglycemia does not allow the cell to switch to lipid oxidation.

Loss of metabolic flexibility is often part of a system-wide dysregulation of metabolism, for instance in type-2 diabetes (T2D) (Corpeleijn et al., 2009). In this context, the most notable effects occur in adipose tissue, muscle tissue, and liver, which develop insulin resistance, and in pancreatic β-cells, which become unable to produce sufficient insulin. In addition, development of T2D results in up-regulation of various pro-inflammatory factors (such as IL-1β, TNF-α, and IL-6, as well as other IL-1 dependent cytokines and chemokines) and activation of their multifactorial transcriptional pathways (Akash et al., 2013), which further enhance metabolic dysfunction. Most of these effects occur in different tissues and are highly interconnected. Thus, studying this in vivo is a considerable challenge, and, especially in the case of systems diseases like T2D, modeling approaches can help in understanding the observable phenotypic changes (Smith et al., 2009) (see Fig. 1).

For instance, in T2D, lower glucose metabolism in pancreatic β-cells has been observed, which leads to reduced secretion of insulin. It has been shown that, in physiological conditions, the rate-limiting step in glucose metabolism is found intracellularly, at the level of glucokinase (the enzyme performing the conversion of glucose to glucose-6-phosphate), which is therefore thought to be an important factor in reduced insulin secretion. However, it is also known that in T2D patients, glucose transporter expression in pancreatic β-cells is reduced, which may also be the cause of lower glucose metabolism. Modeling can help in testing which factor underlies the observed dysfunction. In their model of glucose transport in pancreatic β-cells (Luni et al., 2012) explore the relation between cell surface levels of the glucose transporters GLUT1 and GLUT2 and the rate of intracellular conversion of glucose into glucose-6-phosphate. The authors identify a threshold of receptor expression below which glucose transport becomes limiting to its intracellular utilization, and show that the expression level observed in T2D patients is below this threshold, implying that receptor numbers are at the basis of reduced insulin secretion. The model includes regulation of transporter expression at the transcriptional and post-transcriptional level, which allows the authors to quantitatively study, by sensitivity analysis, the effects of perturbations in different components of the system, thus identifying the most sensitive targets for therapeutic interventions. Extension of this model to include both fatty acid oxidation and the effects of inflammatory mediators, or building of an analogous model for muscle or adipose tissue, could possibly help in identifying important additional points of control for metabolic flexibility.

A multi-compartment approach by Wattis (2007, online report) explores the dynamics of metabolic flexibility, by describing glucose and fatty acid oxidation, and explicitly representing the dynamic interactions between these processes in muscle and blood, as well as the bulk of other organs or tissues. The model is used to study the effects of insulin sensitivity on metabolic flexibility after a meal. As parameter values are only partially available, the authors do not present a full comparison to experimental results. However, their analysis uncovers that insulin insensitivity can dramatically alter the dynamic behavior of the proportion of glucose oxidation after a meal (in a time scale of 30 min to 8 h), reducing both the height of the initial peak in proportion of glucose oxidation and the depth of the subsequent trough. The authors point out that their results could be compared to experimental observations measuring both insulin sensitivity and changes in respiratory quotient (ΔRQ) from fasting to glucose- and insulin-stimulated conditions. This is a typical experimental measure of metabolic flexibility (Galgani and Ravussin, 2008) and could be compared to the magnitude of the peak-trough difference in the model. Additionally, further studies of parameter sensitivities could help in identifying the major processes determining loss of metabolic flexibility, and possibly direct the refinement of the model at the molecular scale.

Although metabolic flexibility is a clearly defined concept (Galgani et al., 2008), with a meaningful translation to experimental settings, it is nonetheless only a partial measure of the functional decline that occurs with aging. In a wider context, one would be interested in quantifying the ability of cells, tissues, systems and whole organism, to adapt to different kinds of stressors, and how this ability declines with aging. Such ability has been termed phenotypic flexibility, and a similar concept has recently been proposed as a definition for health (Huber et al., 2011). Studying the ability of an individual to adapt to a stressor is often done using "challenge tests" and retrieving time resolved data on the response. Several challenges have been developed and are extensively studied in the literature, using either inflammatory stimuli such as lipopolysaccharide (LPS), or nutritional stimuli, as in the oral glucose tolerance test (OGTT), oral lipid tolerance test

(OLTT), or a combination stimulus (Pellis et al., 2012). Except for the OGTT, standardization of nutritional challenges is still not satisfactory (Calder et al., 2013), and is a major focus in the field, since the inflammatory effects are, in this case, more subtle, and thus require stringently controlled experimental conditions. High-throughput methods may be used to comprehensively measure both metabolic and inflammatory responses to challenges (e.g. circulating inflammatory mediators measured by proteomics or multiplex analyses, metabolomics, classical clinical markers, cell counts, and transcriptomics of PBMCs). Response characteristics, as given by, e.g. area-under-the-curve (AUC), peak magnitude, time-to-peak-magnitude, and slope of initial rise, may then be extracted and combined to define measures of "response flexibility", the relevance of which depend on their relation to some other appropriate independent measure of health. One could have, for example, "inflammatory flexibility", defining the ability to adapt the inflammatory response to the nutritional (or inflammatory) stimulus, in accordance with experimental indications of the importance of different temporal characteristics of inflammatory responses to stressors (Beck et al., 2010; Krabbe et al., 2001; Morris et al., 2010). Thus, studying phenotypic flexibility entails defining the dynamic range for the response of a given system (or a set of systems) to a certain stressor (or set of stressors), in physiological and pathological conditions. Mechanistic models of the system carrying out this response, could help in pinpointing, or at least in narrowing down, the specific sites and mechanisms of dysregulation responsible for the different behaviors observed.

5. Strategies for modeling nutritional modulation of inflammation and metabolic flexibility

Metabolism and immunity are fundamental physiological functions which critically depend on one another. While nutritional deficiencies are thought to impair the acute inflammatory response by decreasing the availability of energy and substrates required for appropriate immune defense, overnutrition is thought to promote dysregulation of the physiological dynamics of energy storage and utilization, thereby engaging local inflammatory pathways and impairing metabolic function (Hotamisligil and Erbay, 2008). A proper nutritional intake could therefore be expected to result in an optimally balanced inflammatory response, by not engaging either of these pathological mechanisms.

Quantitative modeling of the interactions between metabolic regulation and inflammatory signaling can help in defining the characteristics that such a diet should have, in terms of energy content, as well as proper macro- and micronutrient balance. Several epidemiological and intervention studies have addressed the effects of dietary factors and patterns on inflammatory parameters and some of their underlying mechanisms of action are known (Calder et al., 2009; Manteiga et al., 2013). Nonetheless, not many mechanistic models have addressed the dynamics of nutritional modulation of inflammation, starting from food intake to downstream effects at the tissue or cellular level. This is a challenging task because of the multiplicity and complexity of intermediate biochemical and biophysical phenomena taking place between nutrient intake and nutrient utilization by different cells and tissues. Given the enormous number of molecular components participating in nutritional, metabolic and inflammatory pathways, it is important to know where mechanistic detail will have added value and where empirical relations will suffice in quantitatively defining interactions (see Box 3). Multiscale models linking molecular, cellular, and whole-organ function, allow for the incorporation of both mechanistic and empirical sub-models at different scales, and may provide a useful framework on which to ground modeling efforts (Scheff et al., 2012; Wu et al., 2009). These models should address the development of a local inflammatory response at the cellular and tissue level, as well as the consequences that the systemic spread of inflammatory mediators has on other organs and tissues and, possibly, on the acute inflammatory response itself. Such an integrative model of nutrition, metabolism and inflammation would allow for a better understanding of how a whole-diet approach manipulates whole-system behavior in a coordinated fashion, help in identifying possible synergistic or antagonistic interactions and allow for in silico testing of the effects of multiple dietary interventions on inflammatory parameters (see Fig. 1).

As for the different time scales of inflammatory processes (inflammaging being the longest scale in this perspective), it would be useful to model the responses of cells and tissues to stimuli of

Box 3. Modeling strategies

The strategy adopted for modeling the behavior of a system depends on the purpose of such modeling effort (Kitano, 2001), as well as on the type and amount of available information regarding the properties of system components and their interactions. In the context of statistical modeling, a model can be used to infer some property of the system from the available data, or to predict future observations given a subset of them (Breiman, 2001). In the former approach, often called explanatory, one typically reasons in terms of the plausibility and interpretability of the model given the available data, whereas in the latter, scrutiny is centered on the accuracy of the model's predictions when given new data. This distinction greatly overlaps with the one between data-driven and hypothesis-driven approaches, where the former are more commonly employed for predictive purposes, and the latter for explanatory purposes. In decision-making contexts, e.g. in diagnostic applications (Haining and Pulendran, 2012), a model with high predictive accuracy is highly desirable, independently of its interpretability; on the other hand, for intervention purposes, i.e. if one wishes to act on the system, then explanatory or causal models may be more useful. Though the same modeling methods, e.g. regression models, may be used in both approaches, more common models for the data-driven approach are neural networks and support vector machines (Hastie et al., 2009), while classical hypothesis-driven models are general linear models, Bayesian models and structural equation models.

Though statistical approaches are capable of including biological domain knowledge in the formulation of a model, they most commonly do so only in a very superficial manner, by hypothesizing about which variables should influence which other variables, and not by deriving the corresponding mathematical relations from biological mechanisms. Mechanistic models, on the contrary, set up the mathematical relations between system components in such a way that the involved parameters have a physical meaning and can potentially be targeted by interventions. Systems spanning several biological scales (intracellular, tissue, system) can generate mechanistic models with hundreds of parameters (Palsson, 2006), appearing in nonlinear mathematical relations (Alves et al., 2008; Gross and Feudel, 2006). This makes parameter estimation a daunting task (Ashyraliyev et al., 2009) and may lead to overfitting and compromise parameter interpretability. It is thus important to make a tradeoff between the detail, or granularity, of the model and its generality. Finally, the frontier between mechanistic and empirical or statistical models is not a sharp one, as all models must develop from a purely empirical basis, which then calls for mechanistic explanations. These explanations may then cast as hypotheses and tested in new experiments, likely to fuel new questions and model refinements, in an iterative manner (Aguda and Friedman, 2008; Beard and Qian, 2008; Szallasi et al., 2010).

different durations and frequencies of repetition. Such stimuli characteristics may be an additional parameter determining the specificity or generality of such responses (Young et al., 2013), and are certainly relevant when prescribing dietary recommendations. Additionally, in the context of both inflammation and metabolism, the simultaneous engagement of fast and slow processes in response to the same stimulus seems to be a common functional pattern, and the study of its long-term consequences could provide insights on the transitions between healthy and pathological states (and vice versa) arising from nutritional stimuli.

Importantly, a certain prescribed dietary intervention will almost certainly have different effects on different individuals. In other words, different individuals may follow different "trajectories" toward improved health, with different "values" on different "axes of function" (inflammatory, metabolic, etc.) (Voit, 2009). These trajectories may depend, for example, on individual genetic make-up or on the initial functional level. A model capable of integrating both of these aspects could be used to disentangle these two sources of variability, to define a normal functional range for each individual (based on dynamic considerations instead of population values) and to help in distinguishing between parameters or variables that are tightly regulated (kept in homeostasis) and parameters that can fluctuate between certain boundaries. Knowing the importance of parameters and individual make-up will help in development of personalized nutrition.

Finally, in the context of aging, and in addition to ectopic fat accumulation, bone and muscle loss may also play important roles in generating low-grade inflammation and metabolic dysfunction; likewise, increasing numbers of senescent cells and alterations in gut microbiota composition are also thought to contribute to inflammaging (Cevenini et al., 2013). These processes may also be taken into account when building an integrative model, but it is outside the scope of this paper to extensively discuss the mechanisms underlying their action.

To summarize, inflammation and metabolism are complex physiological systems whose dysregulation must be understood in terms of their underlying dynamics. Mathematical modeling of such dynamics, with incorporation of mechanistic knowledge on pertinent interactions, may help in devising nutritional interventions capable of preventing, or ameliorating, the age-associated functional decline of these systems.

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