Immunology Letters 162 (2014) 334–345

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Systems Biology and immune aging

José-Enrique O'Connor[a,*], Guadalupe Herrera[b], Alicia Martínez-Romero[c], Francisco Sala de Oyanguren[a], Laura Díaz[a], Angela Gomes[a], Susana Balaguer[a], Robert C. Callaghan[d]

[a] Laboratory of Translational Cytomics, Joint Research Unit, University of Valencia and Principe Felipe Research Center, Valencia, Spain
[b] Laboratory of Cytometry, Incliva Foundation, Clinical University Hospital, University of Valencia, Valencia, Spain
[c] Cytometry Technological Service, Principe Felipe Research Center, Valencia, Spain
[d] Department of Pathology, Faculty of Medicine, The University of Valencia, Valencia, Spain

ARTICLE INFO

Article history:
Available online 22 September 2014

Keywords:
Longevity
Genomics
Proteomics
Metabolomics
Cytomics
Bioinformatics

ABSTRACT

Many alterations of innate and adaptive immunity are common in the aging population, which reflect a deterioration of the immune system, and have lead to the terms "immune aging" or "immunosenescence". Systems Biology aims to the comprehensive knowledge of the structure, dynamics, control and design that define a given biological system. Systems Biology benefits from the continuous advances in the omics sciences, based on high-throughput and high-content technologies, as well as on bioinformatic tools for data mining and integration. The Systems Biology approach is becoming gradually used to propose and to test comprehensive models of aging, both at the level of the immune system and the whole organism. In this way, immune aging may be described by a dynamic view of the states and interactions of every individual cell and molecule of the immune system and their role in the context of aging and longevity. This mini-review presents a panoramics of the current strategies, tools and challenges for applying Systems Biology to immune aging.

1. Immune aging as a system process

Metabolic dysfunction, impaired immune responses to new antigens and inflammation-based disorders are commonly found in the elderly, reflecting the strong link between metabolic regulation and immune responses [1]. Many alterations of innate and adaptive immunity are common in the aging population, which reflect a deterioration of immunity, and have lead to the terms "immune aging" or "immunosenescence" [2]. Many biomarkers of immunosenescence arise from research on T and B cells, which show an altered cytokine pattern, a reduction in clonal expansion and function of antigen-specific T and B cells, and a decline in antigen-presenting cell function. Similarly, the functions of macrophages, neutrophils and natural killer cells, components of the innate immunity, are also decreased [3]. The decline in immune function leads to increased susceptibility of aged individuals to viral, bacterial and fungal infections [4], reactivation of latent viruses and a decreased response to vaccines [5,6].

The relevance of inflammation in the aging process has been consistently confirmed in the recent years, leading to the establishment of the concept of "inflammaging" [2], which identifies the chronic, sub-clinical inflammatory status typical of elderly individuals. Inflammaging coexists with immunosenescence, and indeed several detrimental features collectively denominated as the immune risk phenotype (IRP) [7] have been associated by longitudinal studies on large cohorts of elderly people with increased risk of mortality in Northern Europeans, while centenarians appear to show no IRP [8]. However, recent evidence suggests that inflammaging is in part independent of immunological stimuli and of the total amount of pro-inflammatory mediators, leading to a reappraisal of the involvement of inflammaging in immune senescence of aging, to increase the weight of tissue-environment and cell-type related processes [9]. This novel view shows the importance of identifying the molecular mechanisms that regulate the complex interactions between metabolism and immunity in aging, while reinforcing the need for integrative studies that address the multi-factorial and dynamic factors that explain senescence and longevity.

Aging in experimental and in the humans can be studied at several levels of complexity, from the molecules to the organism and the metaorganism [10–13], as the classical reductive approach, mostly involving molecular and cellular studies may not be

* Corresponding author at: Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Valencia. Av. Blasco Ibañez, 17, 46010 Valencia, Spain. Tel.: +34 963 86 4988; fax: +34 963 86 4001.
E-mail addresses: jose.e.oconnor@uv.es, eoconnor@cipf.es (J.-E. O'Connor).

http://dx.doi.org/10.1016/j.imlet.2014.09.009
0165-2478/

informative enough on the highest levels of biological complexity. Recent knowledge shows that different tissues may age at different but coordinated rates, in the so-called "aging mosaic" [14], resulting from particular combinations of genetic, epigenetic, environmental and stochastic factors, leading to a heterogeneous aging phenotype. In parallel, the recent analytical approaches based in the omic sciences, the high-throughput/high-content methodologies and the power of data mining by bioinformatic tools allow for first time to propose and to test comprehensive models of aging, both at the level of the immune system or the whole organism.

2. Strategies for Systems Biology approach to immune aging

Systems Biology is an emerging discipline that combines high-content, multiplexed measurements with informatic and computational modeling methods to define biological functions at various scales [15,16]. On this basis, Systems Biology is a relatively novel approach in the study of aging and longevity [10–12,17] and the immune system [18–23], as it extends the classical analysis of isolated entities by integrating individual mechanisms and interactions.

The elaboration and testing of comprehensive models in Systems Biology requires complete characterization of an organism in terms of its molecular constituents and their interactions, and how these interactions result in cell function, as well as the spatial and temporal characterization of the molecular responses of the system to external and internal influences. Finally, all such information must be integrated in the form of mathematical models which can be tested by formulating predictions, thus allowing the discovery of new mechanisms and the development of rational strategies for control and manipulation of cells and organisms [5,6,18].

The biological information required by Systems Biology for model building may be gathered either from bottom-up or top-down strategies (Fig. 1). The bottom-up approach involves data collection from different online resources, manual curation of data, simulation of networks through mathematical methods, and validation of generated models by means of literature and database analysis. An example of bottom-up approach is to construct mathematical models from previous kinetics data and predict how a specific protein contributes to aging and antiaging processes These approaches allow researchers to simulate the effect of each gene product in aging by in silico genetic manipulations, such as deletion or over-expression [16,24,25].

The 'top-down' strategy is the most frequent in Systems Biology [16]. It starts from a general view of the behavior of the system by providing large and complex omics data, and aims to discover and to characterize biological mechanisms regulating the components and their interactions. Top-down strategies may be potentially complete (i.e., genome-wide) and address the entire levels of biological complexity (metabolome, fluxome, transcriptome, proteome and cytome). A typical example of top-down approach in aging studies would be to predict the role of a specific gene in the aging process by comparing its expression profile and protein–protein interaction pattern with those of known longevity genes. Most currently available studies on immune aging and senescence follow 'top-down' strategies [10–12,17].

3. Tools in Systems Biology

3.1. Genomics and metagenomics

3.1.1. Transcript profiling

Transcriptomics implies the study of the complete set of RNAs (transcriptome) produced by the genome of a specific cell or organism at a specific time and/or under a specific set of conditions. Transcriptomic approaches using microarrays and, more recently, RNA sequencing, have been applied repeatedly to the study of aging in humans and in animal models [14].

Most transcriptomic studies are aimed to identify genes that are differentially expressed with chronological age, and in many cases, have been focused on blood samples [26] but many of the expression changes found in human blood have also been found in genes related to lymphocytes and the immune system [27]. Signatures of aging have been also found to be consistent across tissue and species [28] and the gene pathways showing most altered gene expression with age were related to the immune response, including complement activation, antigen processing, apoptosis and anti-apoptosis. Some studies have compared normally aging individuals with younger patients with progeria syndromes and have found similarity in the majority of age-related expression changes [29].

Transcriptomics study of total RNA in blood mononuclear cells (PBMC) of healthy young and middle-age versus healthy old individuals showed that quantitative changes of expression were accessible biomarkers of aging. Some differential expression, like CD28, CD69, LCK (decreased abundance in old subjects), CD86, Cathepsins D, H and S (increased abundance in old subjects) reflected the low-grade pro-inflammatory status in old persons and suggested a reduced response of T-cells together with an increase in antigen presentation potential. In addition, genes involved in the oxidative stress response were found more active in PBMC from elderly subjects [30].

3.1.2. Next generation sequencing

The array-based transcriptomic studies are limited in part by the lack of sensitivity to low abundance transcripts and by the issue of inter-laboratory reproducibility due to the use of different microarray platforms, as shown by multicentric studies using different platforms but identical RNA samples [31].

Current gene expression array data are also limited in that they do not provide information on microRNAs (miRNAs). Part of these limitations may be overcome by the use of RNA sequencing approaches, as shown recently by comprehensive comparison of transcriptome analysis obtained by RNA-sequencing and microarrays [32].

Next generation sequencing (NGS) uses massive parallel analyses of individually amplified DNA fragments [33]. NGS systems process beyond 1 gigabase of sequence per run. In this way, genome-wide analyses allow to extend sequencing the entire genome by specialized determinations, such as the quantitative analysis of expressed mRNA, epigenetically-modified DNA, nucleic acid bound to a specific protein, or DNA sensitive to enzymatic degradation.

NGS has been recently applied to explore the basic principles of immune-receptor repertoire selection, and its relation to disease and vaccination. The size, diversity, and affinity of this repertoire are closely linked to the immune response and, likely, may be affected by aging. Hence, exploring this diversity and its clinical implications in an individual or a population is of high importance. Through the design of primers flanking regions of interest deep sequencing of antibody and TCR sequences [34], as well as of HLA regions [35], have been obtained.

A recent study [36] has applied high-throughput long read sequencing to perform immunogenomic characterization of expressed human antibody repertoires in the context of influenza vaccination. Informatic analysis of 5 million antibody heavy chain sequences from healthy individuals showed that elderly subjects have a decreased number of lineages but an increased pre-vaccination mutation load in their repertoire and that some of these subjects have an oligoclonal character to their repertoire in which