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Signaling networks in focus

The signaling hubs at the crossroad of longevity and age-related disease networks

Marina Wolfson, Arie Budovsky, Robi Tacutu, Vadim Fraifeld*

The Shraga Segal Department of Microbiology and Immunology, Faculty of Health Sciences, Center for Multidisciplinary Research in Aging, Ben-Gurion University of the Negev, P.O. Box 653, Beer-Sheva 84105, Israel

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ABSTRACT

The established human age-related disease proteins (ARDPs) and longevity-associated proteins (LAPs) together with their first-order interacting partners form scale-free networks which significantly overlap. About half of the common proteins are involved in signal transduction. These proteins are strongly interconnected and in turn form a common signaling network which comprises over 40% of all hubs (proteins with multiple interactions) in the human interactome. Along with the insulin pathway, the common signaling network is remarkably enriched with the focal adhesion and adherens junction proteins whose relation to the control of lifespan is yet to be fully addressed. The examples of such candidate proteins include several hubs, focal adhesion kinase PTK2 and the extracellular proteins fibronectin FN1, paxillin PXN, and vinculin VCL. The results of the network-based analysis highlight the potential importance of these pathways, especially hubs, in linking the human longevity and age-related diseases.

1. Introduction

Hundreds of genes have been identified as being involved in human age-related diseases (ARDs) and in the control of lifespan in model organisms (Budovsky et al., 2007, 2008 and references therein). These studies highlight that aging, longevity, and ARDs are associated with multiple genetic factors. Yet, the trend to focus on individual genes and/or their products continues to dominate, reflecting in part a paradigm in biomedical research—searching for the specific targets that offer the potential for the development of highly specific drugs. In spite of enormous efforts and accumulated knowledge, our capabilities for tackling aging and ARDs, and ultimately promoting longevity are very modest. What is lacking—the essential knowledge of key players or efficient analytic tools, or both? Here we discuss how the existing data may be integrated and analyzed using a network-based approach, focusing specifically on the role of signaling proteins and pathways in linking the human longevity and ARDs.

It has become increasingly clear that biological systems function as complex networks (Barabasi and Oltvai, 2004), indicating that the properties of the system could not be reduced to the properties of its components (though they are also important). Furthermore, the network's topology may determine the system's behavior which otherwise cannot be deduced by using the reductionistic approach. Most biological networks examined so far and, in particular, protein–protein interaction (PPI) networks, exhibit scale-free topology. This topology is characterized by the presence of few nodes with a considerable number of connections (hubs) while the majority of nodes have only a few connections. The scale-free topology causes the network to become a structure that is highly resistant to random node failure but mainly vulnerable to the removal of hubs (Barabasi and Oltvai, 2004). Thus, the scale-free topology generates network robustness, allowing the system to respond and adapt to changes in external or internal conditions without losing its normal functionality and integrity. Moreover, scale-free networks own a remarkable evolutionary advantage of being able to evolve rapidly towards specific functions dictated by natural selection (Oikonomou and Cluzel, 2006).

A good example of a PPI scale-free network is the human interactome. Currently, it includes about 8000 proteins with more than 23,500 experimentally established PPIs. Over one third of all PPIs are attributed to hubs (defined here as most connected nodes with $\geq$40 connections) which comprise only 1.5% of proteins in the interactome.

2. Common signaling signature network of human longevity and major age-related diseases

Could the longevity-associated proteins (LAPs) or ARD proteins (ARDPs) be organized as networks? Recently, such a possibility

* Corresponding author. Tel.: +972 8 6477292; fax: +972 8 6477626.
E-mail addresses: vadim.fraifeld@gmail.com, fraifeld@bgu.ac.il (V. Fraifeld).

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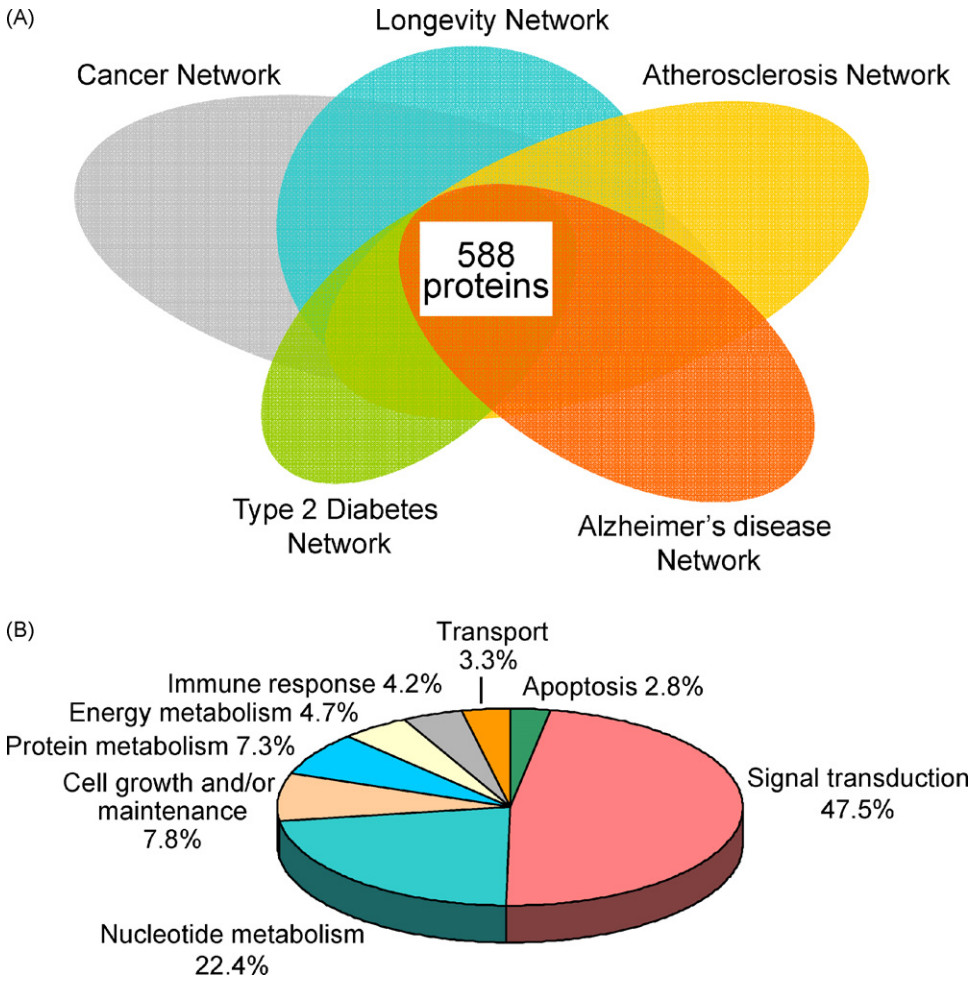

Fig. 1. Common signature network (CSN) of genes/proteins associated with longevity and major age-related diseases. The criteria for selection of longevity-associated genes/proteins and those involved in cancer were described in details elsewhere (Budovsky et al., 2007, 2008). The same criteria as for cancer-associated genes/proteins were used for collecting the genes/proteins associated with atherosclerosis, Alzheimer's disease, and type 2 diabetes. These data were collected from scientific literature and from publicly available databases including the Cardiovascular Bioinformatics Database – Cardio (http://cardio.bjmu.edu.cn/), AlzGene database (http://www.alzforum.org/res/com/gen/alzgene/default.asp), and Type 2 Diabetes Mellitus Database – T2D-Db (http://t2ddb.ibab.ac.in/). (A) Schematic representation of the overlap between the human longevity network and the networks of major age-related diseases. (B) Distribution of CSN proteins by basic processes. The proteins were classified using annotation from the human protein reference database (HPRD) (http://www.hprd.org/). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

has been shown by us for the human orthologs of LAPs identified in the model organisms, the human cancer proteins and also for the proteins involved in Alzheimer's disease, type 2 diabetes, and atherosclerosis (for details see Budovsky et al., 2007, 2008). The established human ARDPs and LAPs together with their first-order interacting partners form scale-free networks with an extremely high contribution of hubs to the network connectivity. These networks actually represent sub-networks of the human interactome which significantly overlap one another (Fig. 1A). The common overlap ("common signature") consists of 588 proteins and displays several remarkable features:

- First, almost all common signature proteins (98%) interact between themselves. Thus, the common signature can be actually defined as a common PPI network of longevity and major ARDs (common signature network; CSN).
- Second, the CSN is significantly enriched with signaling proteins (Fig. 1B) compared with the whole human interactome (48% versus 29%, respectively; $p < 5.1E{-}06$) or any other ARD network or human longevity network (HLN). The signaling proteins of the CSN are strongly interconnected and in turn form a scale-free network (further denoted as a common signaling signature network; CSSN; Fig. 2).
- Third, approximately three quarters (92 of 126; 73%) of all hubs in the human interactome are concentrated in the CSN; of them, more than a half (55 of 92) are signaling proteins. Many signaling proteins in the CSN and especially the hubs are key "switchers" or "connectors" between different signaling pathways, thus assuring the cross-talk between the pathways and their coordinated functioning (Fig. 2).

Epidemiological observations indicated clear evidence of the impact of ARDs on longevity in humans. Indeed, the incidences of ARDs including atherosclerosis, cancer, type 2 diabetes, and neurodegenerative pathology increase in advanced age and they still are the main factor limiting the human lifespan (Cutler and Mattson, 2006). The above network analysis supports the idea that the mechanisms of major ARDs and those that regulate longevity, have much in common. The results also highlight that the molecular links between longevity and ARDs are, to a great extent, mediated through the signaling proteins.