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Editorial commentary: Nuclear receptors and a network biology approach to understanding and treating heart disease

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A pivotal insight refined in the era of "omics" and big data is that human disease is seldom caused by the actions of a single molecular alteration but, instead, arises via multiple pathobiological pathways that interact through complex networks [1]. A complete map of interacting molecules in living systems is far from being fully defined, but we now have an increasingly rich conceptual understanding of the human "interactome" composed of protein coding genes, post-translationally modified proteins, functional (non-protein-coding) RNAs, carbohydrate and lipid macromolecules, and the myriad small molecules of intermediary metabolism and biological signaling. All told, this probably encompasses more than 100,000 different molecules, a daunting prospect as one imagines the number of potential interactions and networks that might be at play in the pathogenesis of human disease [1]. Nevertheless, the emerging science of network biology has revealed that cellular networks are highly clustered, and a reasonably manageable number of evolutionarily conserved proteins fulfill critical roles in maintaining networks and organizing complex biological functions, both in health and disease [1]. It is in this context that we should consider nuclear receptors, a topic highlighted in a paper in this issue of *TCM* [2].

The human genome encodes a family of 48 nuclear receptor proteins [3,4]. These include steroid hormone receptors, nuclear receptors that heterodimerize with retinoid X receptors, and a group of proteins, representing approximately half of the family, referred to as "orphan" receptors because their ligands, if they exist at all, are not known. Nuclear receptors are transcription factors - they have the ability to bind DNA and change gene expression. Their discovery by Pierre Chambon and Ronald Evans, who, respectively, cloned the estrogen and glucocorticoid receptors in the 1980s, and Elwood Jensen, who had isolated the estrogen receptor decades earlier, was recognized in 2004 with the Albert Lasker Award for Basic Medical Research. These investigators, and many others who followed, sought to understand how steroid and thyroid hormones and lipid-soluble vitamins (e.g., vitamins A and D) regulate complex physiologic processes [3]. Despite the chemical diversity of these ligands, it turned out they shared a similar signaling mechanism involving intracellular receptors (in the cytosol or nucleus), which after binding ligand, activated transcription of tissue-specific target genes. The surprising finding that followed identification of the first steroid hormone receptors in the1980s was the existence of nearly 50 evolutionarily related proteins for which, in many cases, the associated small molecule ligands were unknown. Despite their "orphan" status, however, these nuclear receptors are highly conversed throughout metazoan evolution (they are not found in protozoans, fungi or plants) and they fulfill fundamental roles as integrators and coordinators of signaling networks required for multicellular life [3].

All of the nuclear receptors, including the orphans, contain a central DNA-binding domain with which they interact with the genome to control gene transcription, and a carboxyl-terminal domain that forms a canonical ligand-binding pocket in which various small non-protein molecules including steroid hormones, retinoids, cholesterol derivatives and fatty acids bind and activate nuclear signaling [3]. The amino acid sequences of their N-terminal domains, involved in protein-protein interactions, diverge considerably reflecting the potentially vast array of proteins with which individual nuclear receptors communicate [3].

This issue of *TCM* features a review by Vivian de Waard on the NR4A family of nuclear receptors and their role in cardiac remodeling and neurohormonal regulation [2]. The NR4A family includes Nur77 (also known as NR4A1, TR3 or NGF1-B), Nurr1 (NR4A3) and NOR-1 (NR4A3). They have no known ligands. Analysis of their crystal structures shows that their ligand-binding domains contain no apparent cavity but are instead filled with bulky hydrophobic residues [4]. Thus, they are thought to be ligand-independent and constitutively active – the idea is that their ability to regulate gene expression depends on their expression level, post-translational modifications and specific protein-protein interactions. A recent study, however, challenges this notion and suggests that the ligand-binding pocket is dynamic and can expand from the collapsed crystalized conformation to one that allows binding of unsaturated fatty acids [5]. Whether NR4A receptors are truly orphans or have ligands thus remains an open question which, in a more general sense, raises the possibility of still to be discovered signaling pathways activated by still to be discovered ligands.

What do NR4A nuclear receptors do in the heart and what roles do they play in heart disease? Here is where we encounter a level of complexity that compels interpretation of complex heart disease using systems biology and network medicine approaches. NR4As are immediate-early response genes [4]. Their expression is rapidly induced by stress, and they are activated by numerous

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stimuli including growth factors, cytokines, and hormones. As detailed in de Waard's review, one or more of the NR4A nuclear receptors regulates the expression and/or activities of genes responsible for production of virtually all of the major players in the sympathetic neurohormonal and renal-angiotensin-aldosterone systems that control cardiovascular function in health and disease [2]. They do this by regulating gene expression not only in cardiac myocytes but in the central nervous system, adrenal chromaffin cells, bone-marrow derived immune cells, and adipose tissue. In all of these tissues, they act to regulate the production and degradation of many other transcription factors and coregulatory proteins. Nur77 alone interacts with more than 80 proteins [5], and the other NR4A members likely have their own unique sets of interacting proteins. Through such integrating and coordinating interactions in cardiac, neural, endocrine and immune cells, they thus contribute, directly and/or indirectly, to the control of myocardial contractility, heart rate, hypertrophic cardiac growth and remodeling, myocardial fibrosis, blood pressure, sodium and water homeostasis, and immune signaling in the heart [2].

NR4As are only the latest class of nuclear receptors to be recognized as master regulators of cardiovascular function. Others fulfill similarly fundamental roles integrating normal and pathological processes in the heart. For example, the peroxisome proliferator-activated receptors, PPARα and PPARδ, are ligand-activated nuclear receptors that serve as master regulators of myocardial metabolism [6]. Their ligands include a wide range of fatty acids and through such binding interactions they oversee ATP production in the heart. During development, PPARs coordinate the conversion from anaerobic metabolism of glucose as the primary fuel for ATP production during fetal life to oxidative phosphorylation of fatty acids in the adult heart [6]. As fatty acid oxidation ramps up in the postnatal period, PPARs orchestrate a surge in mitochondrial biogenesis and autophagy required for the high level of ATP production in the adult heart. In pathological settings, PPARs mediate the switch back to glucose and lactate as an energy source in the failing heart [6]. They also play a major role in diabetes and related metabolic disorders. It comes as no surprise, therefore, that PPARs and the pathways they control are targets of several drugs in wide clinical use. Additional classes of nuclear receptors that regulate cardiac function include those activated by sex hormones, thyroid hormone, and vitamins A and D. Other yet to be discovered ligands and signaling pathways may come into play as well.

How, then, do we understand nuclear receptors in terms of regulatory function, as mediators of disease, and as targets for new drugs? The answer, of course, is the emerging field of network biology, which provides a functional framework for understanding interconnections – cellular, biochemical, genetic – obtained from increasingly powerful high-throughput profiling of normal human biology and disease [1]. Such interactions can be organized into "nodes" from which a few highly interactive "hubs" often emerge, typically representing proteins encoded by ancient, evolutionarily conserved genes, that function to maintain the integrity of the network and play crucial roles in basic cellular processes. Using this approach, disease modules can be constructed in which known disease genes are merged with the human interactome to define specific sub-networks that encompass a large number of disease-associated factors and functional pathways [1]. This explanation is, of necessity, an overly simplified description of the process but such approaches are now being used to identify new disease genes and pathways and improve rational drug discovery. Recent examples include discovery of new disease genes (and potential new drug targets) in cardiac hypertrophy and failure through network analysis of gene expression modules active during both cardiac development and disease [7], use of network analysis to understand how GATA4 mutations contribute to congenital heart disease [8], and a systems biology approach explaining how microRNA-21 regulates pathogenic pathways in pulmonary hypertension [9].

The field of network biology is still in its infancy. Its major limitation is incomplete knowledge of interactome maps, but ongoing discoveries will fill the gaps and enable this strategy to realize its full potential. The NR4A nuclear receptor family and its role in cardiovascular pathobiology is a new piece of the puzzle. Certainly, more must be done and learned but, for now, it is appropriate to designate the emerging recognition of NR4A nuclear receptors as high-level mediators of heart disease a trend in cardiovascular medicine.

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