Molecular and Cellular Endocrinology ■■ (2014) ■■–■■

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Review

Botanical compounds and their regulation of nuclear receptor action: The case of traditional Chinese medicine

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ARTICLE INFO

Article history:
Received 3 October 2014
Received in revised form 23 October 2014
Accepted 31 October 2014
Available online

Keywords:
Nuclear receptor
Traditional Chinese medicine
Pharmacology
Agonist
Antagonist

ABSTRACT

Nuclear receptors (NRs) are major pharmacological targets that allow an access to the mechanisms controlling gene regulation. As such, some NRs were identified as biological targets of active compounds contained in herbal remedies found in traditional medicines. We aim here to review this expanding literature by focusing on the informative articles regarding the mechanisms of action of traditional Chinese medicines (TCMs). We exemplified well-characterized TCM action mediated by NR such as steroid receptors (ER, GR, AR), metabolic receptors (PPAR, LXR, FXR, PXR, CAR) and RXR. We also provided, when possible, examples from other traditional medicines. From these, we draw a parallel between TCMs and phytoestrogens or endocrine disrupting chemicals also acting via NR. We define common principle of action and highlight the potential and limits of those compounds. TCMs, by finely tuning physiological reactions in positive and negative manners, could act, in a subtle but efficient way, on NR sensors and their transcriptional network.

Contents

Abbreviations: AR, androgen receptor; CAR, constitutive androstane receptor; DBD, DNA-binding domain; EDC, endocrine disrupting chemical; ER, estrogen receptor; FXR, farnesoid X receptor; GR, glucocorticoid receptor; HRE, hormone responsive elements; LBD, ligand-binding domain; LXR, liver X receptor; NGF-IB, nerve growth factor-IB; NR, nuclear receptor; NURR1, nuclear receptor related 1; PPAR, peroxisome proliferator activated receptor; PXR, pregnane X receptor; RAR, retinoid acid receptor; RXR, retinoid X receptor; SERM, selective estrogen receptor modulator; SHP, small heterodimer partner; SNuRMs, selective nuclear receptor modulators; SRC, steroid receptor coactivator; TCM, traditional Chinese medicine; TR, thyroid receptor; VDR, vitamin D receptor.

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http://dx.doi.org/10.1016/j.mce.2014.10.028
0303-7207/

1. Traditional medicines and herbal compounds

Since plants are at the origin of western pharmacopeia, we can say that traditional medicines were a major source of the modern pharmaceutical industry. An important approach of western medicine has been to use the therapeutic effect of plants in order to identify the active molecule and to chemically synthetize it. In many cases, studying the derivatives of such compounds allowed to improve the efficacy or specificity of the biological effect (Corson and Crews, 2007). This is the case of the well-known aspirin, derived from salicylic acid present in the bark of willow trees (genus *Salix*) traditionally used to treat fever and inflammation. In modern western medicine the purification of single molecules is in fact a prerequisite to the marketing of a drug. Indeed, to register a drug, one should have a single molecule with a well-characterized biological effect on specific targets that should be used to treat a specific disease. By contrast to this reductionist approach, traditional medicine rely on the effects observed by complex mixtures of molecules obtained directly from crude plant extracts. This is well exemplified by traditional Chinese medicine (TCM). In this review, we will focus on botanical compounds from TCM because it is one of the most ancient and commonly used medicines with a well-defined medical corpus. Indeed, from the "Divine Farmer's *Materia Medica*" (Shen Nong Ben Cao Jing, 神农本草经), the oldest Chinese book on agricultural and medical plants that describes more than 300 traditional Chinese drugs (Wang et al., 2007), to the "Compendium of *Materia Medica*" (Ben Cao Gang Mu-本草纲目), the most complete and comprehensive text written by Li Shi Zhen in the sixteenth century (Tian and Huang, 2007), an abundant and ancient Chinese medical literature is still the source of remedies in the treatment of many diseases (May et al., 2012). Currently, almost 100,000 TCM preparations using 11,000 kinds of herbs, 300 minerals and animal extracts are used in China to treat more than 3700 diseases (Qiu, 2007). Furthermore, TCM has gained increasing attention from the western health-care systems (Scheid, 1999), which raises important issues regarding the scientific nature of some of its practices. Our approach could be fruitfully applied to other traditional medicines, and we provide some examples. However, an exhaustive analysis of all traditional medicine would be beyond the scope of this synthesis.

An important principle used to prepare TCM drug is to restore the internal balance by combining ingredients, which is thought to be more effective than application of a single compound (Chen et al., 2010). This illustrates very well the major conceptual and practical differences between western medicine (based on single compound isolation) and TCM (based on the combination of several ingredients). TCM compound formulae (fufang) (Fig. 1) contain several plants, among which one represents the active component (the sovereign), and the others serve as adjuvant to assist the effects (additivity, synergy) or to facilitate the delivery (detoxification, compatibility) of the principal component (Tian, 2011).

It is thought that multiple components can hit multiple targets and exert synergistic effects with less toxicity than one purified compound (Li and Zhang, 2008). This combination therapy is more complex than biomedical pharmacology and therefore it has rarely been scientifically tested. As an example, the Realgar-*Indigo naturalis* formula (RIF) has been proven to be effective in treating human acute promyelocytic leukemia (APL), a cancer induced by the fusion protein PML-RARα. An arsenic sulfide mineral (*realgar*) is the principal element of RIF, while three plants (*Indigo naturalis*, *Salviae miltiorrhizae* and *Pseudostellaria heterophylla*) play the role of adjuvants. It is the combination of tetraarsenic tetrasulfide (As_4S_4), indirubin (from *Indigo naturalis*), and tanshinone IIA (from *Salvia miltiorrhizae*) that yields synergy in the treatment of a murine APL model *in vivo* (Wang et al., 2008). This use of arsenic to treat APL in TCM is striking, given that arsenic trioxide combined with retinoic acid is now a treatment of choice in western medicine to cure APL and indeed the use of arsenic for such a purpose was pioneered in northern China (Lo-Coco et al., 2013; Shen et al., 1997).

Nevertheless, such promising examples are rare and raise several questions regarding the future of TCM. First, how do mixtures of ingredients act in concert? Indeed, in contrast with western pharmacology, the active compounds and their mechanisms of action are usually unknown for TCM products, which treat the symptoms rather than the cause of disease (Chan, 1995). That is why "westernization" of TCMs is considered as a necessary step to understand their principles of action. This is a huge task, if we consider that almost 7000 compounds have already been isolated from TCM formulae, acting on more than 17,000 targets (Chen, 2011; Xue et al., 2013). A successful example of such an approach is artemisinin (qinghaosu), a new antimalarial drug, which was isolated from *Artemisia annua*, a plant used in China for almost 2000 years in the treatment of malaria (Wang et al., 2007; Miller and Su 2011; Tu Youyou 2011). Because TCM has a holistic approach, system biology and –omics technologies are probably the most appropriate ways to understand the mechanisms that underlie the therapeutic effects of these mixtures (Qiu, 2007; Tian, 2011). Recent projects go in this direction, such as "Fangjiomics" that aims to identify and design effective mixtures of bioactive agents and elucidating their modes of action (Wang et al., 2011), while "Chinmedomics" refers to the metabolomics of TCM formulae (Wang et al., 2012a). Large non-commercial TCM databases have been constructed to support those efforts (Chen, 2011; Xue et al., 2013). Another concern is that the use of TCM has sometimes been associated with adverse effects, such as hepatotoxicity (Chen et al., 2011). As for any herbal treatment, variations in geographical or seasonal growth locations and harvest time have potential impacts on toxicity and safety of the product (Li et al., 2005; Wu et al., 2007). It is also known that drug-drug interactions can have detrimental effects, sometimes strongly decreasing the effect of a remedy. It is therefore important to separate whenever possible the active compounds eliciting the beneficial from the toxic compounds. Finally, because TCM use wild plants, the availability, quality and stability of raw material are variable and often limited (Chan, 1995). Furthermore, some of these plants are rare or threatened with extinction (Li and Vederas, 2009). This is not a minor issue if you consider that more than 25,000 TCM herbal ingredients are prepared from more than 11,000 species of plants (Qiu, 2007). The same problem exists for ingredients of animal origin and the role of Chinese medicine in the extinction of prominent species (e.g. rhinoceros, tiger etc.) has often been highlighted (Graham-Rowe, 2011). If one can identify efficient and synthesizable compounds, then it would be useful for the protection of plants and biodiversity and also benefits human beings. These considerations on TCMs can also be applied to other traditional medicines that use mixtures, mostly of herbal origins. It is actually an important aim of ethnobotany to identify these complex relationships between human cultures and the medical use of plants.

The modernization of TCMs is not only to search for single compounds but also to evaluate the synergistic mechanisms of composite formulae. Therefore, an "easternization" of western medicine may

Please cite this article in press as: Ling Li, François Bonneton, Xiao Yong Chen, Vincent Laudet, Botanical compounds and their regulation of nuclear receptor action: The case of traditional Chinese medicine, Molecular and Cellular Endocrinology (2014), doi: 10.1016/j.mce.2014.10.028