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Review

The functional genomic studies of curcumin

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ABSTRACT

Curcumin is a natural plant-derived compound that has attracted a lot of attention for its anti-cancer activities. Curcumin can slow proliferation of and induce apoptosis in cancer cell lines, but the precise mechanisms of these effects are not fully understood. However, many lines of evidence suggested that curcumin has a potent impact on gene expression profiles; thus, functional genomics should be the key to understanding how curcumin exerts its anti-cancer activities. Here, we review the published functional genomic studies of curcumin focusing on cancer. Typically, a cancer cell line or a grafted tumor were exposed to curcumin and profiled with microarrays, methylation assays, or RNA-seq. Crucially, these studies are in agreement that curcumin has a powerful effect on gene expression. In the majority of the studies, among differentially expressed genes we found genes involved in cell signaling, apoptosis, and the control of cell cycle. Curcumin can also induce specific methylation changes, and is a powerful regulator of the expression of microRNAs which control oncogenesis. We also reflect on how the broader technological progress in transcriptomics has been reflected on the field of curcumin. We conclude by discussing the areas where more functional genomic studies are highly desirable. Integrated OMICS approaches will clearly be the key to understanding curcumin's anticancer and chemopreventive effects. Such strategies may become a template for elucidating the mode of action of other natural products; many natural products have pleiotropic effects that are well suited for a systems-level analysis.

1. Introduction

Curcumin is a dietary polyphenol derived from the rhizomes of the plant *Curcuma longa* increasingly recognized for its strong anti-tumor, anti-inflammatory [1] and cancer chemopreventive properties. Curcumin may also have a protective role in cardiovascular diseases; this includes both chronic conditions such as atherosclerosis [2] and acute cardiovascular events such as myocardial infarction [3]. Curcumin also has strong putative antioxidant effects: it can both directly neutralize free radicals and induce body's antioxidant enzymes [1,4]. Curcumin may be also beneficial in arthritis [5,6], neurodegenerative diseases [7,8] and autoimmune conditions [9]. Many aspects of the biology of curcumin have been already reviewed (for example its pharmacodynamics [10], biological activities [10,11], molecular targets [12,13], chemopreventive properties [12], or anti-tumor effects [12,14]). Here, we focus on the functional genomics studies of the anti-cancer activities of curcumin.

Existing data suggest strong anti-cancer effects of curcumin, especially on gastrointestinal tumors. For example, curcumin has confirmed chemopreventive effects in the mouse and rat models of carcinogenesis of colon cancer, intestinal cancer, stomach cancer, and hepatocellular carcinoma [15–22]. In particular, Rao et al. [16] showed that dietary curcumin inhibited colon carcinogenesis induced by the carcinogen azoxymethane in rats. However, the precise molecular mechanisms by which curcumin exerts such chemopreventive effects are yet to be elucidated.

So how does curcumin work? There is already a lot of evidence that curcumin works by modifying gene expression profiles (reviewed in [23]). These changes in expression patterns are probably secondary to curcumin's primary effects on transcription factors and the proteins of cell signaling pathways. Nevertheless, understanding how curcumin modifies gene expression is the key to understanding curcumin's impact on the living cell.

Thus, it is clear that expression profiling with functional genomics can help to unravel the modes of action of curcumin. These actions can be studied both *in vitro* and *in vivo* using a number of platforms, reflecting the progress in the technology of functional genomics (Fig. 1). The typical *in vitro* workflow is illustrated in Fig. 2. Typically, an analysis consisted of the following four phases: (i) *in vitro* cell culture, incubation with curcumin/RNA isolation, (ii) microarray hybridization and readout, (iii) bioinformatics, and (iv) experimental verification.

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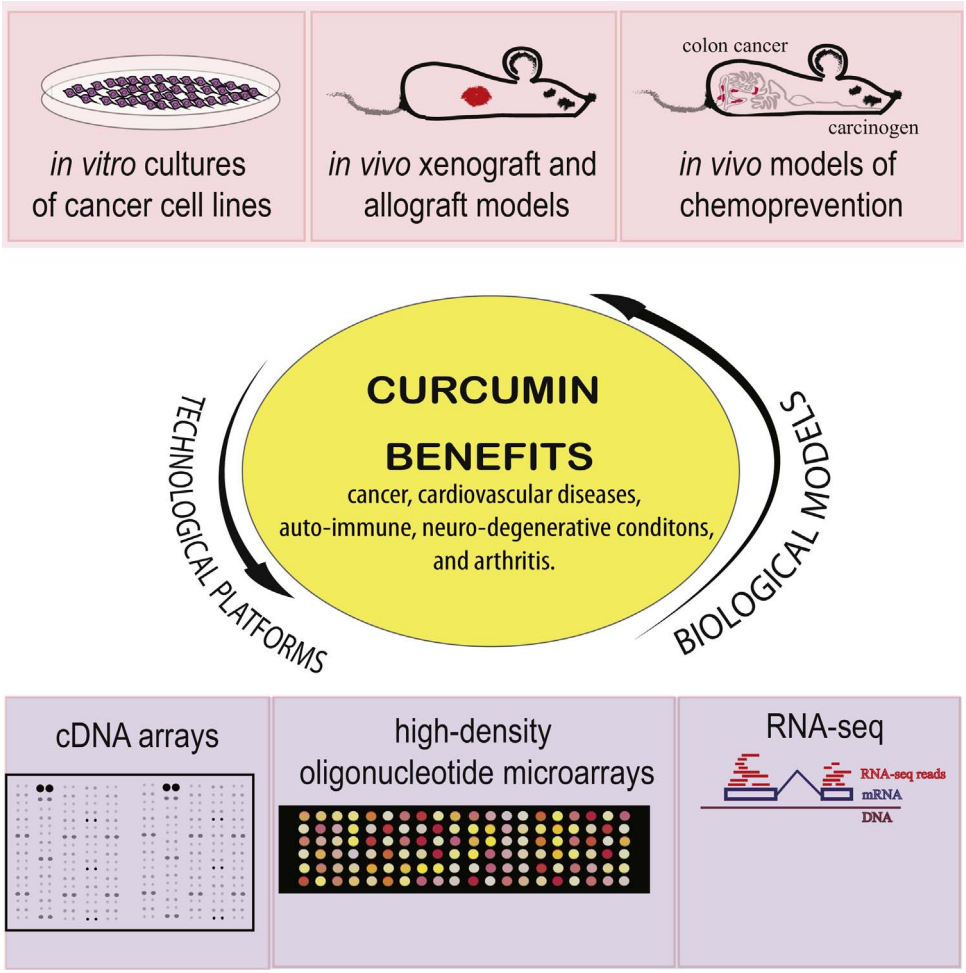

Fig. 1. The major themes of the functional genomics of curcumin.The effects of curcumin can be studied either *in vitro* or *in vivo* biological models (illustrated in the upper part of the figure). In both cases, anti-cancer or anti-inflammatory effects of curcumin are of greatest interest. Here, we focus exclusively on the anti-cancer effects. These effects fall into two broad classes: (i) the direct inhibitory effects of curcumin on the pathological phenotypes of cancer cells; or (ii) chemopreventive effects – that is curcumin applications that aim to delay, inhibit, or reverse carcinogenesis. The growing interest in curcumin's anti-cancer effects has been accompanied by technological progress in functional genomics (illustrated in the lower part of the figure). At first, the researchers used low-density spotted arrays of cDNA clones (Table 2). Later, commercial high-density oligonucleotide-based microarrays became available (Table 2). As the interest in regulatory RNAs was growing, researchers also profiled microRNAs (Table 3). Finally, technologies based on next generation sequencing, such as RNAseq, became available (Table 3).

Curcumin has direct effects on signaling pathways in addition to its effects on gene expression. In particular, curcumin affects several signaling pathways known to represent important pathogenic pathways for solid and blood cancers: such as the PI3k/Akt-1/mTOR pathway [24–27], the Ras/Raf/MEK/ERK pathway [25], the GSK-3beta pathway [28]. Curcumin as also been shown to exhibit anticancer properties via the activation of p53 [29]. Finally, curcumin suppresses NF-kappaB [30] activation and blocks expression of enzymes promoting inflammation such as cyclo-oxygenase-2 [31,32].

We note dissenting voices on the clinical usefulness of curcumin. Several reviews pointed out the low bioavailability of curcumin in tissues after oral administration, suggesting that efficacy outside the gastrointestinal tract may be limited [33–35]. The same reviews also underlined the lack of large successful randomized clinical trials of curcumin. Some metabolites of curcumin may be pro-oxidative in high concentrations. Moreover, the purported impact of curcumin on many signaling proteins may be due to its non-specific tendency to interfere with protein assays [35]. In our opinion, however, the controversy only enhances the motivation to study curcumin using functional genomics. (If curcumin's protein interactions can be non-specific, it makes sense to focus on curcumin's impact on gene expression and genome methylation).

Here, we review the functional genomics studies of curcumin focusing on cancer research (Fig. 3, Table 1). The studies were identified by searching Medline, the Web of Science, and Gene Expression Omnibus.[1] Our goal was to draw conclusions about the common mode of action of curcumin, despite different technological platforms and biological models. We use footnotes to provide details while preserving the flow of narrative in the main text. Our approach may be of general interest as functional genomics is making an impact on the study of many anti-cancer compounds. (Indeed, OMICS may be irreplaceable for the study of compounds with pleiotropic effects).

2. First studies used simple low-density cDNA arrays

Our review will retrace the path of the broader technological progress in the field of functional genomics. We start by considering four early studies published between 2000 and 2005. These studies used the older types of low-density custom-printed microarrays to

[1] We considered only functional genomics datasets that were accompanied by a publication in a journal belonging to the Web of Science Core collection. Only for such studies could we retrieve journal impact factor and the number of citations (Fig. 2, Table 1).

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