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Review

Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds

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ABSTRACT

The association between chronic inflammation and cancer development has been well documented. One of the major obstacles in cancer treatment is the persistent autocrine and paracrine activation of pro-inflammatory transcription factors such as nuclear factor-κB, signal transducer and activator of transcription 3, activator protein 1, fork head box protein M1, and hypoxia-inducible factor 1α in a wide variety of tumor cell lines and patient specimens. This, in turn, leads to an accelerated production of cellular adhesion molecules, inflammatory cytokines, chemokines, anti-apoptotic molecules, and inducible nitric oxide synthase. Numerous medicinal plant-derived compounds have made a tremendous impact in drug discovery research endeavors, and have been reported to modulate the activation of diverse oncogenic transcription factors in various tumor models. Moreover, novel therapeutic combinations of standard chemotherapeutic drugs with these agents have significantly improved patient survival by making cancer cells more susceptible to chemotherapy and radiotherapy. In this review, we critically analyze the existing literature on the modulation of diverse transcription factors by various natural compounds and provide views on new directions for accelerating the discovery of novel drug candidates derived from Mother Nature.

1. Introduction

Cancer remains a major health issue and is the second leading cause of morbidity world-wide with an incidence rate of 2.6 million cases per year [1,2]. Most existing anticancer therapies not only provide limited therapeutic advantage to the patients but are also associated with significant adverse effects [3,4]. Natural products contribute significantly in the anticancer drug discovery process by serving as important leads for the development of novel therapies [5,6]. The majority of United States Food and Drug Administration (US FDA) approved entities reveals that natural products and their derivatives occupy one-third of all novel drugs [7,8]. These

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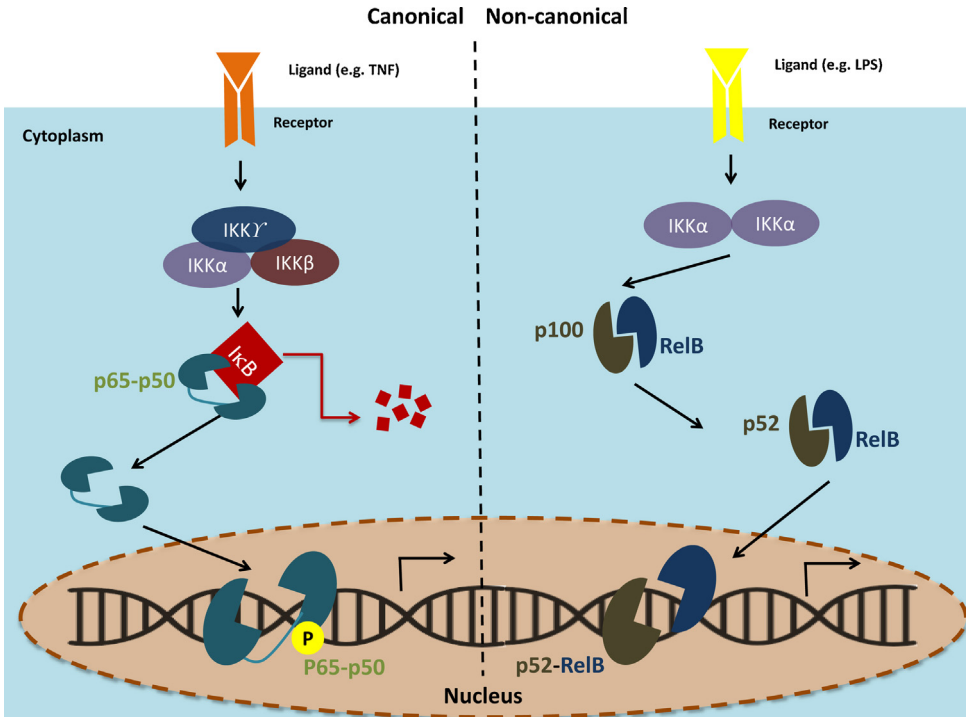

Fig. 1. NF-κB expression is tightly regulated and aberrant activity has been linked to tumorigenesis. In unstimulated cells, NF-κB dimers are present within the cytoplasm and its activity is sequestered by a family of inhibitors known as IκBs. In the canonical signaling pathway (left), the binding of a ligand (e.g. TNF) to its cognate receptor leads to the eventual recruitment of the IKK complex. IKKγ is phosphorylated (p), leading to the release of IKKα and IKKβ, which targets and degrades IκB. The p65-p50 dimers are released and translocated into the nucleus with the aid of transport proteins such as importin, which acts on its regulatory elements. In the non-canonical pathway (right), a select set of cell-differentiating or developmental stimuli activates NF-κB activity. The p100 subunit is further processed into p52, which re-dimerizes with RelB and translocates into the nucleus. Comparatively, canonical NF-κB signaling relies on phosphorylation and degradation of IκB, while the non-canonical NF-κB signaling is dependent upon the p100 subunit being processed into p52.

natural compounds generally exhibit multi-targeted effects and can affect diverse oncogenic targets including transcription factors, cytokines, chemokines, adhesion molecules, growth factor receptors, and inflammatory enzymes [4,9,10].

Epidemiological, preclinical, and clinical studies have indicated that the process of chronic inflammation plays a vital role in both the initiation and development of carcinogenesis [11,12]. Chronic inflammation has been reported to mediate various key steps involved in tumorigenesis, including cellular transformation, survival, proliferation, invasion, angiogenesis, and metastasis. Within the tumor microenvironment, inflammation generally contributes to favorable conditions that promote both the development of genomic aberrations as well as the initiation of carcinogenesis. While acute inflammation has been associated with therapeutic implications, the inadequate resolution of persistent inflammatory responses can lead to various human malignancies [11,12].

Among the various molecular targets, transcription factors not only act as an important link in coupling the process of chronic inflammation to that of cancer but also play a critical role in tumor initiation and progression [13]. Hence, a majority of natural products including curcumin, resveratrol, epigallocatechin gallate (EGCG), emodin, celastrol, honokiol etc., have been reported to modulate several oncogenic transcription factors including nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), nuclear factor (erythroid-derived 2)-like 2 (Nrf-2), fork head box protein M1 (FoxM1), peroxisome proliferator associated receptor gamma (PPARγ), hypoxia-inducible factor 1α (HIF1α), Wnt/β-catenin, activator protein 1 (AP-1), c-Met, also known as hepatocyte growth factor receptor(HGFR), and Hedgehog (Hh/GLI) in diverse tumor cell lines, mouse models, and clinical samples [4]. The primary focus of this review is to briefly discuss the potential of a few important natural products in regulating proliferation, survival, and metastasis of tumor cells via modulation of oncogenic transcription factors, and to analyze the potential molecular mechanism(s) that contribute to their reported anticancer effects.

2. Transcription factors

In normal cells, transcription is a tightly controlled process and is critical for normal cellular proliferation and differentiation. In contrast, in tumor cells, signaling proteins regulating various transcription factors are often deregulated and are the major source for diverse oncogenic changes in functions of these proteins. These include uncontrolled cellular proliferation, anti-apoptosis, metastasis, multidrug resistance and radioresistance [4,9,10].

Multiple oncogenic transcription factors such as NF-κB, STAT3, Wnt/β-catenin, FoxM1, HIF1α, and Hh/GLI are often deregulated in cancers and promote initiation, promotion and progression of the malignant cells. Thus, these transcription factors constitute important molecular targets for chemoprevention and treatment of cancer.

2.1. NF-κB

The pro-inflammatory transcription factor, NF-κB, regulates the expression of numerous genes that promote uncontrolled cellular proliferation and survival that is frequently constitutively activated in various tumor cells (Fig. 1) [14–19]. Many phytochemicals have been identified in recent years that have demonstrated significant inhibitory effects on NF-κB signaling cascades through diverse mechanism(s) in various tumor models [20,21]. The chemical structures of few selected natural compounds discussed in this article that can target NF-κB as well as other major oncogenic signaling cascades in tumor cells is shown in Fig. 2. Curcumin, a natural agent

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