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Invited Review

Targeting activator protein 1 signaling pathway by bioactive natural agents: Possible therapeutic strategy for cancer prevention and intervention

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ABSTRACT

Activator protein 1 (AP-1) is a key transcription factor in the control of several cellular processes responsible for cell survival proliferation and differentiation. Dysfunctional AP-1 expression and activity are involved in several severe diseases, especially inflammatory disorders and cancer. Therefore, targeting AP-1 has recently emerged as an attractive therapeutic strategy for cancer prevention and therapy. This review summarizes our current understanding of AP-1 biology and function as well as explores and discusses several natural bioactive compounds modulating AP-1-associated signaling pathways for cancer prevention and intervention. Current limitations, challenges, and future directions of research are also critically discussed.

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Contents

1. Introduction

A complex network of signaling pathways is responsible for cellular proliferation, behavior and death in multicellular organisms [1]. Identification of the molecular mechanism is essential for understanding the pathogenesis and underlying factors of any disease process. Research for the discovery of drugs targeting cancer has gained tremendous importance in last few decades. Recently, activator protein 1 (AP-1) has attracted a fair share of attention as a novel drug target for cancer. AP-1 is a key transcription factor which regulates several cytological processes, including differentiation, cell death, proliferation, oncogenic transformation, apoptosis, and cell migration during development as well as in adult tissues [2]. AP-1 is a dimeric transcription factor that binds to the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) response element (TRE) for the transcriptional activation of target genes which are responsible for the regulation of these processes and have a crucial role in the tumorigenic process [3,4]. The mammalian AP-1 proteins belong to the members of Jun (JunB, c-Jun, and JunD), musculoaponeurotic fibrosarcoma (Maf) [MafA, MafB, c-Maf, MafG/F/K and Nrl], Fos (Fra-1, Fra2, c-Fos, and FosB) and activating transcription factor (ATF) sub-families (e.g., ATF2, LRF1/ATF3, B-ATF, JDP1, JDP2) [5–7]. They form homo- and hetero-dimeric complexes that bind to DNA by interacting with basic leucine zipper (bZIP) domain [8]. In addition, AP-1 proteins can also interact with other proteins beyond bZIP, including the p65 subunit of nuclear factor-κB (NF-κB), CREB-binding protein (CBP)/p300, and retinoblastoma tumor suppressor protein (Rb), thus increasing the variety of AP-1 family proteins and the regulated genes [9]. Various natural compounds target these subfamilies to elicit their effects in various disease conditions.

The role of an AP-1 complex is also very important in the insatauration and/or progression of several pathological conditions, including inflammatory processes, cancer, rheumatoid arthritis, psoriasis, transplant rejection, and asthma [2,7,10–13]. AP-1 also modulates the activation of different immune cells and controls cytokine expression at multiple levels in genetically engineered mouse models in the absence of AP-1 [10].

AP-1 transcription factor may be activated by various factors, including chemokines, growth factors, cytokines, environmental stresses, and hormones. Activation of AP-1 by Jun-N-terminal kinases (JNKs) cascade is an example for such activation. This process involves the stress-responsive mitogen activated protein kinases (MAPKs) pathways [14]. MAPKs are subcategorized into three subfamilies, namely Jun N-terminal kinases (JNK)/stress-activated protein kinase (SAPK), extracellular signal-regulated kinases (ERK1/2), and p38 MAPK [15,16]. ERK5/BMK1 (big MAPK1) is another MAPK that has been identified [17,18]. MAPKs pathways are eventually accountable for the activation and phosphorylation of Jun and Fos proteins [14]. This suggests that activation of AP-1 may lead to the tumor progression resulting through activation and phosphorylation of MAPKs pathways. Thus, targeting AP-1 and other associated proteins can be of immense importance in combating disease conditions including inflammation and cancer.

Considering the importance of AP-1 signaling pathway, in this review, we first explore the molecular mechanism of action of AP-1. Further, we postulate that AP-1 can also be targeted by several bioactive natural products. Therefore, we tried to explore various phytochemicals that could modulate the AP-1 signaling pathways in various oncologic diseases. To the best of our knowledge, this is the first attempt to focus on AP-1 targeting natural products in cancer prevention and treatment.

2. Regulation of AP-1 and its targets

Here we describe regulation pathways of AP-1 that have some unique ability in the process of cell proliferation. The activation of AP-1 depends on dimmer composition, transcription and post-translational modification and the potential interaction with other proteins. Additionally, the activity of AP-1 complexes is modulated by AP-1 protein phosphorylation and gives a route to extracellular stimuli for the regulation of AP-1 activity [19,20]. The proto-oncogenes c-Fos and c-Jun are immediate-early genes that are transiently expressed in response to a variety of stimuli. The products of these genes can interact via bZIP to form heterodimers that bind specifically to AP-1 [21–23]. In this sense, the c-Fos transcription and status of c-Jun phosphorylation have been reported to mainly regulate the AP-1 activity in T-cells [21–23]. The positive regulation of cell proliferation is the unique ability of c-Jun amongst other Jun proteins. This takes place via downregulation of tumor suppressor genes and induction of transcription cyclin D1, a key regulator of G_1 to S phase transition [19]. On contrary, JunB induces upregulation of tumor suppressor genes and downregulates cyclin D1[19]. AP-1 also contributes in TPA-inducible [24] and basal gene expression [25]. AP-1 activity is also induced by various other stimuli, such as oncoproteins, like Ha-Ras or v-Src [3], tumor necrosis factor-α (TNF-α) [26], interleukin-1 (IL-1) [27,28], growth factors [29–31], and most conspicuously serum [30,32]. AP-1 together with NF-κB also plays a role in the regulation of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, and they are considered crucial for the induction of genes which are involved in the inflammation process [33–35]. This shows the importance of AP-1 in the modulation of oxidative stress through iNOS expression.