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Novel natural product therapeutics targeting both inflammation and cancer

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[ABSTRACT] Inflammation is recently recognized as one of the hallmarks of human cancer. Chronic inflammatory response plays a critical role in cancer development, progression, metastasis, and resistance to chemotherapy. Conversely, the oncogenic aberrations also generate an inflammatory microenvironment, enabling the development and progression of cancer. The molecular mechanisms of action that are responsible for inflammatory cancer and cancer-associated inflammation are not fully understood due to the complex crosstalk between oncogenic and pro-inflammatory genes. However, molecular mediators that regulate both inflammation and cancer, such as NF-κB and STAT have been considered as promising targets for preventing and treating these diseases. Recent works have further demonstrated an important role of oncogenes (*e.g.,* NFAT1, MDM2) and tumor suppressor genes (*e.g.,* p53) in cancer-related inflammation. Natural products that target these molecular mediators have shown anticancer and anti-inflammatory activities in preclinical and clinical studies. Sesquiterpenoids (STs), a class of novel plant-derived secondary metabolites have attracted great interest in recent years because of their diversity in chemical structures and pharmacological activities. At present, we and other investigators have found that dimeric sesquiterpenoids (DSTs) may exert enhanced activity and binding affinity to molecular targets due to the increased number of alkylating centers and improved conformational flexibility and lipophilicity. Here, we focus our discussion on the activities and mechanisms of action of STs and DSTs in treating inflammation and cancer as well as their structure-activity relationships.

[KEY WORDS] Cancer; Inflammation; Sesquiterpenoid; MDM2; p53; NF-κB

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Introduction

There is an increasing interest in investigation of the relationships between inflammation and cancer. We and others have proposed to dually target molecules involved in both inflammation and cancer as a novel approach to cancer prevention and treatment. Inflammation is the body's protective response to microbial infection and other environmental stimuli, which usually cause tissue damage. Consequently, infection-triggered inflammatory response causes the destruction of damaged tissues and stimulates its regeneration [1-2]. It has been recognized that acute inflammation contributes to tumor regression while chronic inflammation plays a crucial role in tumor initiation and progression [3-4]. Indeed, more than one fifth of human cancers are associated with chronic and dysregulated inflammation [4]. Chronic inflammation is commonly featured by the persistent activation of immune system, which inevitably results in the accumulation of genetic and epigenetic aberrations, and consequently leads to malignant transformation [4-5]. During this procedure, many molecular mediators, including cytokines [*e.g.,* tumor necrosis factor (TNF)-α and interleukins (ILs)], transcription factors [*e.g.,* nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3)], tumor suppressor genes (*e.g.,* p53) and oncogenes [*e.g.,* murine double minute 2 (MDM2)] are involved in the tumor inflammatory microenvironment; most of the mediators (Fig. 1) have been extensively discussed in recent reviews [5-7]. Here, we focus on the

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recently uncovered mediators that are involved in inflammation and cancer as well as the changing paradigms in the field.

NF-*κ*B and STAT are well-documented pro-inflammatory transcription factors that play critical roles in inflammation and cancer [8-9]. After activation by pro-inflammatory stimuli, NF-*κ*B regulates the transcription of most of the genes related to inflammation [*e.g.,* TNF, ILs, chemokines, and cyclooxygenase 2 (COX-2)] as well as survival genes in cancer cells [*e.g.,* c-Myc, cyclinD1, and B-cell lymphoma-extra large (Bcl-xl)] [8]. STAT activation contributes to parts of IL-6's functions and promotes cancer cell proliferation and tumorigenesis [9]. Recent studies have indicated that NF-*κ*B and STAT3 collaboratively control the communication between cancer cells and inflammatory cells [9]. Nuclear factor of activated T-cells (NFAT), which was initially discovered in human T cells, has been demonstrated to play an important role in the regulation of inflammatory response, development and metastasis of cancer, and other biological events in the human body [10-11]. Hypoxia-inducible factor 1 (HIF1) exerts a well-established role in cancer initiation and progression and is essential for the execution of an optimal inflammatory response [12]. The complex cross-talks (Fig. 1) among NF-*κ*B, STAT3, NFAT, and HIF1 in immune cells and tumor cells have yet to be fully comprehended. All of these transcription factors have been demonstrated as promising targets for the treatment of inflammation and cancer.

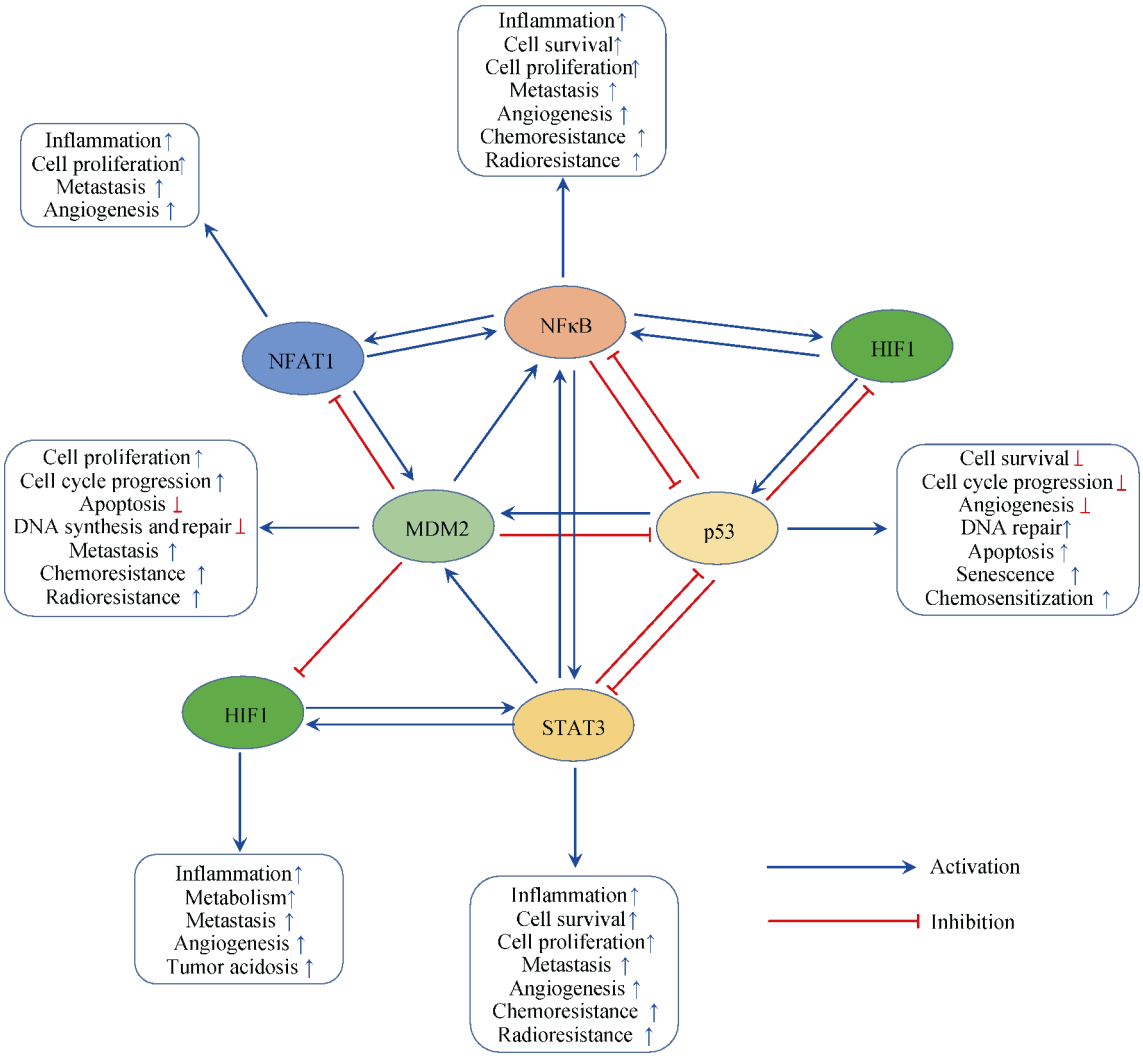

Fig. 1 Key mediators of inflammation and cancer that are targeted by STs and DSTs

The MDM2 oncogene and the p53 tumor suppressor gene continue to hold interest as therapeutic targets in human cancers [13-14]. Many MDM2 inhibitors and p53 activators have been developed for the treatment and prevention of human cancers; several of them have currently entered clinical trials [13-16]. Recent studies have shown that MDM2 plays an important role in inflammation and inflammatory diseases via both p53-dependent and p53-independent mechanisms (Fig. 1) [17-21]. MDM2 inhibitors have also been reported to exert potent anti-inflammatory effects in tissue injury by inhibiting NF-*κ*B [17, 21-23]. Because both p53 and NF-*κ*B p65 exert their transactivation activities by interacting with p300/CREB-binding protein