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2'-Hydroxycinnamaldehyde: a potent inhibitor of AP-1 and NF-κB, stimulation of cell proliferation and suppression of apoptosis in turmorigenesis

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2'-Hydroxycinnamaldehyde (HCA) is a hydroxyl derivative of cinnamaldehyde isolated from the bark of Cinnamomun cassia Blume, which has been shown to induce apoptotic cell death and growth inhibition of several human cancer cell lines. However, little is known about the possible mechanism of cell death and growth inhibition. To determine the putative action mechanisms of growth inhibition in cancer cell lines, we investigated the inhibitory effect of HCA on the signal pathway protein leading to activation of NF-κB and AP-1 in SW620 cells. Treatment of SW620 colon cells with HCA (10, 20, 40, 80 μM) inhibited cell growth in time- and dose-dependent manner, and increased the induction of apoptosis in a dose dependent manner. HCA also inhibited MAP kinase signaling cascade leading to phosphorylation of AP-1 transcriptional activity. TNF-α, IL-1 and IL-6 can act as growth and survival factors in a variety of malignancies and NF-κB promotes turmorigenesis by suppression of apoptosis and stimulation of cell proliferation. In TNF-α induced SW620 colon cells, HCA also inhibited cell growth and NF-κB activation in dose-dependent manner. NF-κB dependent transcription in NF-κB transfected cells also was inhibited by HCA at micromolar concentrations. Inhibition of NF-κB activation seems to be specific since other DNA-binding activities were not affected. These results demonstrate that HCA inhibits cell growth through inhibition AP-1 activation, whereas, HCA induces apoptosis by NF-κB inactivation in SW620 colon cells.

Introduction

Cinnamomum cassia has been widely used for treating dyspepsia, gastritis, and inflammatory diseases. We previously isolated a cinnamaldehyde derivative, 2'-hydroxycinnamaldehyde

(HCA), from the stem bark of *Cinnamomum cassia*, and found it has an inhibitory effect on farnesyl transferase activity *in vitro* [1]. In addition, we also found that 2'-hydroxycinnamaldehyde has several other activities such as anti-angiogenic activity [2], immunomodulating activity [3], and also has to induce apoptotic cell death and growth inhibition of several human cancer cell lines including breast, leukemia, ovarian, lung, and colon tumor cells [4]. However, little is known about the possible mechanism of cell death and growth inhibition. To determine the putative action mechanisms of growth inhibition in cancer cell lines, we investigated the inhibitory effect of HCA on the signal pathway protein leading to activation of NF-κB and AP-1 in SW620 cells.

For a long time, oncogenesis has been viewed as the result of unlimited proliferation of tumor cells, which is certainly at the core of this process [1]. Many oncogenes were identified by virtue of their ability to induce uncontrolled cell proliferation [1]. Proto-oncogenes or tumor suppressor genes are often the components of signaling pathways involved in proliferation or cell division, thereby stimulating cell growth [1–3]. Compelling evidence shows that the other side of the coin, programmed cell death (apoptosis), is likely to play an equally important role in oncogenesis [4–6]. The transcription factor NF-_B is a key regulator of immune responses and inflammation operating through the induction of numerous genes, including those coding for cytokines, chemokines and adhesion molecules [7,8]. NF-_B may also be involved in oncogenesis. Many oncogenes can activate NF-_B, whose activity is required for subsequent transformation [9,10]. Furthermore, the viral counterpart of NF-_B, v-Rel, is highly oncogenic [11]. This notion is consistent with the discovery that NF-_B induces expression of cell cycle regulators such as cyclin D1 [9]. The analysis of NF-_B deficient mice and cells led to the identification of a novel function for this versatile transcription factor—the inhibition of apoptosis [12]. As shall be discussed later, the anti-apoptotic function of NF-_B is tightly linked to its oncogenic activity. Several recent reviews have described the role of NF-_B in oncogenesis with respect to its function in promoting cell proliferation and transformation [9,10].

First discovered and studied as a major activator of immune and inflammatory function via its ability to induce expression of genes encoding cytokines, cytokine receptors, and cell-adhesion molecules [1,2], the transcription factor nuclear factor (NF)-κB recently has been linked to control of cell growth and oncogenesis. The roles for NF-κB in cancer appear to be complex, but are likely to involve the ability of this transcription factor to control apoptosis and cell-cycle progression, and possibly cell differentiation, angiogenesis

and cell migration. Importantly, it has been reported that NF-κB is activated in cancer cells by several chemotherapies and by radiation, and that in many cases this response inhibits the ability of the cancer therapy to induce cell death [3]. Here, we discuss the potential for the development of inhibitors of NF-κB as primary as well as adjuvant approaches to cancer therapy.

The process by which a normal, healthy cell becomes a tumour involves multiple steps over an extended period of time, as described for colon cancer by Fearon and Vogelstein [3]. To achieve full malignancy, cells must acquire certain transforming characteristics [4], including (1) self-sufficiency in growth signalling and limitless replicative potential, (2) becoming unresponsive to antiproliferative signals, (3) evading apoptosis, (4) inducing and sustaining angiogenesis, and (5) acquiring the ability to invade and metastasize. This sequence of events presents many opportunities for intervention, with the aim of preventing, slowing down or reversing the tranformation process (Fig. 1). Ideally, chemoprevention would halt the carcinogenic process at an early stage, perhaps even preventing the formation of preneoplastic lesions.