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Editorial

Molecular Targets, Cancer Chemoprevention, and Dietary Phytochemicals: Nuclear Annexin A1 as a Promising New Molecular Target of Cancer Chemoprevention

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Abstract

Allosteric modulation of G protein-coupled receptors (GPCRs) confers several significant advantages over the traditional targeting of orthosteric sites. While the field of allosteric modulation of GPCRs as we now know it will benefit from continued investigation, the explosion of interest has led to a more in-depth understanding as to precisely how allosteric modulators may usher in a new paradigm for drug discovery.

While conventional treatments with anti-cancer drugs and surgical operations following early diagnosis have recently improved the survival of patients with various cancers, they do not influence the incidence of cancers. Therefore, prevention of cancers among populations of risks such as diets and anti-hormone agents is still an urgent and important issue. The goal of cancer chemoprevention is to suppress or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer. Carcinogenesis results from accumulated genetic and epigenetic mutations, and alterations take place in multiple signaling pathways for proliferation and angiogenesis. In addition, cancer formed is frequently mixed populations in various stages of cellular differentiation. Accordingly, molecular mechanisms of carcinogenesis provide targets of cancer chemoprevention.

It is generally estimated that 30-40% of cancers are directly linked to diet-related factors [1]. However, how specific dietary components impact cancer risk is not fully understood, although many phytochemicals derived from plants are now reported to interfere with certain stages of the carcinogenic process [2]. These stages include multisteps in the pathways to carcinogenesis, epigenetic modulation such as histone acetylation and methylation and DNA methylation, and transcription factor pathways, e.g. NFkB and AP1 [2,3,4]. Despite of reports on positive effects on a variety of steps in carcinogenesis *in vitro* and *in vivo*, few protective effects against carcinogenesis with these phytochemicals have been firmly established.

Molecular mechanisms involved in carcinogenesis provide strong rationales for developing cancer treatments and prevention. Chemoprevention and chemotherapy of cancers frequently share common targets and goals. These include the suppression of NFkB and AP1 activation pathways, inhibition of tumor cell proliferation pathways, down-regulation of cyclooxygenase -2 expression, epigenetic modulation, suppression of angiogenesis and so on. Major clinical successes of cancer chemoprevention are brought by vaccines targeting infection of viruses such as hepatitis B and human papilloma virus, risk factors for hepatocellular cancer and cervical cancer. Some molecular targeted agents can also prevent breast cancer (tamoxifen and raloxifene), prostate cancer (finasteride) and colon cancer (celecoxib). However, the wide ranges of chemicals including phytochemicals are not yet translated to the clinic [5].

Annexin A1, a 37kDa protein previously reffered as lipomodulin or lipocortin I, was first discovered as a phospholipase A_2 inhibitory protein that mediates an anti-inflammatory action of glucocorticoids [6]. Since this protein contains a SH2 like sequence, thus being a major substrate of oncogenic tyrosine kinases such as *c-met* and *c-src*, it is thought that annexin A1 is involved in signaling of growth factors and/or mitogens for cell proliferation-differentiation [7,8]. Thus, it is proposed that annexin A1 has some regulatory roles in cancer development. However, expression of annexin A1 is increased in certain types of cancers such as pancreas and bladder cancers, while it is reduced in other types of cancer including breast and prostate cancers. Annexin A1 is generally present in cytosols and membranes, but is also found in nuclei of proliferating cells. Nuclear translocation of annexin A1 requires tyrosine phosphorylation and Ca^{2+} signaling, and is promoted by oxidative stress and DNA damaging agents [9]. Nuclear annexin A1 is modified with SUMO related peptides and DNA damage signals promote its conversion to mono-ubiquitinated form. Quantitative proteomic study also indicates that annexin A1 plays an important role in DNA damage response [10]. Therefore, nuclear annexin A1 is closely associated with turmorigenesis and propression, while changes in total cellular expression of annexin A1 may not be involved in cancer development.

Mono-ubiquitinated annexin A1 has a DNA helicase activity, and exhibits higher affinity for damaged DNA such as DNA containing 8-oxoguanosine. As a result, this form of annexin A1 1 promotes translesion DNA synthesis by error-prone DNA polymerases such as Polβ [9]. These observations suggest that annexin A is involved in DNA damage-induced mutagenesis [11]. Indeed, anti-sense oligonucleotide against annexin A1 can reduce mutation frequency in L5178Ytk(+/-) cells treated with methanesulfonate (MMS) and $As^{3}+$. Since DNA damage induced mutation is a key event in initiation of carcinogenesis, we proposed that annexin A1 in nuclei is a promising molecular target for cancer chemoprevention. Supporting this hypothesis, flavonoids, dietary chemopreventive compounds, are

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found to bind to annexin A1 and to inhibit MMS, As^{3+}-induced mutations of L5178Ytk (+/-) lymphoma cells [12]. Advantage of selecting annexin A1 as a molecular target of cancer chemoprevention is to rationally design inhibitors by measuring DNA helicase activity rather than applying *in vivo* and/or *in vitro* animal and cellular model systems for cancer initiation. If successful, such inhibitors are expected to be effective for prevention of broad ranges of cancers, since DNA damage induced mutagenesis is thought to be a common pathway of initiation of various cancers.

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