MicroRNA: A New Player for Cancer Chemoprevention

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In 2012, a total of 1,638,910 new cases and 577,190 deaths from cancer are projected to occur in the United States [1]. From 2004 to 2008, the overall cancer death rate was decreased by 1.8% in men versus 1.6% in women yearly, which may result from the successful implementation of early detection, treatment, and prevention methods [1]. Although its potential has not yet been fully realized, chemoprevention by using pharmaceuticals (e.g. anti-inflammatory drugs) to retard or reverse the process of carcinogenesis and progression of cancer has been recognized to benefit individuals with precancerous lesions or with genetic susceptibility to cancer [2-4]. The concept of chemoprevention encompasses all stages of disease progression including the prevention of tumor initiation through DNA repair, detoxification, free-radical scavenging, and carcinogen metabolism; prevention of tumor promotion by inhibiting proliferation or inducing differentiation or apoptosis; and the inhibition of tumor progression by suppressing tumor cell invasion and metastasis [5].

Tumor metastasis is a hallmark of malignant disease that is often responsible for chemotherapy failure and death of the patient. It was estimated that only 6% of breast cancer patients have detectable metastatic disease at the time of diagnosis and surgery [6]. Thus, prevention of tumor cell invasion and metastasis represents a largely unexplored target for chemoprevention in patients with malignant disease who are at risk of disease progression. Due to poor understanding of the mechanistic basis that accounts for this complex biological process, there are very few therapeutic and preventive drugs have been discovered that can be successfully used to treat cancer patients with metastasis in clinic.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are a chemically diverse family of drugs commonly used to treat a variety of inflammatory conditions and pain associated with arthritis. The long-term use of NSAIDs has been shown to significantly reduce the incidence and risk of death from colorectal and other forms of cancer [7]. Sulindac, in particular, has been shown to display strong efficacy for the treatment of precancerous lesions in patients with Familial Adenomatous Polyposis (FAP) in which treatment can suppress adenoma size and number by as much as 60-70% [8]. These observations are consistent with a large number of preclinical studies that have shown the ability of sulindac and other NSAIDs to inhibit tumorogenesis and tumor progression in various experimental animal models [9-12]. For example, Moon et al. found that sulindac was able to induce the expression of thrombospondin-1 (TSP-1) and early growth response gene-1(Egr-1) by using the Min mouse model, both of which were considered to play a role in the suppression of tumor cell invasion [13]. The study by Kundu et al. showed that celecoxib (COX-2 inhibitor), SC560 (COX-1 inhibitor), and the non-selective COX-1/2 inhibitor (indomethacin), could inhibit not only tumor cell growth, but also metastasis in vivo [14]. A recent LANCET publication reported that daily use of aspirin could reduce the risk of death from tumor metastasis by up to 48% based on meta-analyses of a large number of randomized controlled clinical trials [15]. Therefore, NSAIDs have a potential to prevent tumor metastasis and disease progression and the use of NSAIDs should be a viable option for cancer patients with advanced diseases.

MicroRNAs (miRNAs) are naturally occurring, single-stranded, and non-coding sequences of small RNAs that bind to 3’-UTR of target genes to repress their expression at the post-transcriptional and translational levels [16,17]. Nearly 30% of all human genes are regulated by miRNAs in which each is capable of mediating the expression of several hundred cognate messenger RNA targets simultaneously [18]. Approximately 2,000 human miRNAs have been characterized that are involved in many biological processes including apoptosis, proliferation, differentiation, tumorigenesis, and metastasis [19-22]. We recently reported in ONCOGENE that sulindac sulfide (SS) can inhibit tumor cell invasion by a distinct mechanism from its COX inhibitory activity [23]. By using microarray analysis, we found that SS treatment could alter the expression of 132 miRNAs (17 up and 115 down) in human colon cancer HCT116 cells at sub-toxic concentrations. Several of these miRNAs are of particular interest to us, such as miR-10b, -17, -21, and -9, because they have been previously reported to promote tumor metastasis and invasion [24-30]. In addition, we demonstrated that inhibition of NF-κB by SS is an important mechanism attributing to suppression of these oncogenic miRNAs [23]. As the inhibitory effect of SS on tumor cell invasion was proved to be associated with dramatic changes in miRNA expression, we concluded that miRNAs are involved in the anti-metastatic activity of sulindac [23].

Although miRNA has been involved in the pathogenesis of variable human cancer types and are significantly associated with the clinicopathological parameters and treatment responses, its important roles in cancer chemoprevention have not yet been well studied. Given that miRNAs are recognized as the master gene expression regulators and the changes of their multiple target genes are tightly associated with almost all cellular events, miRNAs may account for the mechanistic basis of NSAIDs’ complex pleotropic antineoplastic activities. Therefore, studying miRNA in cancer chemoprevention is of novelty and significance for discovering and developing safer and more efficacious antineoplastic drugs in the future.

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References


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