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MicroRNAs involve inhibition of tumor progression by NSAIDs

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Abstract

Although mechanisms of the action have yet been well-understood, non-steroidal anti-inflammatory drugs (NSAIDs) are widely reported to display strong efficacy for cancer prevention. The most known anti-cancer activities of NSAIDs include inhibition of tumor cell proliferation and induction of apoptosis, but their effects on tumor progression and metastasis have not been well studied. Here, we show that the NSAID, sulindac sulfide (SS) can potently inhibit the invasion of human MDA-MB-231 breast and HCT116 colon tumor cells *in vitro* at concentrations less than those required to inhibit tumor cell growth. When studying the molecular basis for this activity, we found that SS can inhibit the translocation of NF-κB to the nucleus by decreasing the phosphorylation of IKKβ and IκB. NF-κB is one of the most known transcription factors and regulates expression of numerous genes including microRNAs. After we explored the global microRNA profile of HCT116 tumor cells by using microarray analyses, a total of 132 microRNAs were found to be altered (17 up and 115 down) in response to SS treatment, including miR-17-92 cluster, miR-10b, miR-21 and miR-9, which have been previously implicated in tumor progression and metastasis. Our data show that these microRNAs can significantly promote tumor cell invasion but SS can inhibit these oncogenic activities by suppressing their expression at transcriptional level. Analysis of the promoter sequences of 115 microRNAs suppressed by SS revealed that 81 of them contained NF-κB-binding sites. Employing chromatin immunoprecipitation (ChIP) assays, we confirmed that NF-κB could bind the promoters of miR-17-92 cluster, miR-10b, miR-21 and miR-9. In addition to validation of several published metastatic suppressors targeted by these microRNAs, such as TβR, HOXD10, TPM1, and PDCD4, we identified a novel marker QKI that is co-targeted by these oncogenic microRNAs and responsible for the inhibitory effect on tumor cell invasion by SS. In summary, our results show that microRNAs and their target genes involve inhibition of tumor progression by the NSAID sulindac.

Biography

Yaguang Xi got the Ph.D from Peking University after his clinical training. He is an Assistant Professor at the University of South Alabama Mitchell Cancer Institute. To date, Dr. Xi has authored 43 publications in many prestigious journals and is serving as the member of editorial board and ad-hoc reviewer for many journals and grant agencies.