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Choosing the right carrier for siRNA-based applications-A new reporter system which acts by induction of endogenous intracellular fluorescence

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A new detection mechanism for the control of successful siRNA delivery to cells or tissue is introduced using a siRNA-based probe that is capable of inducing a specific intracellular fluorescence emission. Protoporphyrin-IX (PpIX) is a fluorescent metabolite of heme-synthesis. Every nucleated human cell requires heme for heme-containing enzymes essential for the cellular energy metabolism. The last step of heme synthesis is incorporation of iron into PpIX that takes place in the mitochondria catalyzed by the enzyme ferrochelatase (FECH). Experimentally induced knock down of FECH expression in tumor cells by RNA-interference (siRNA) leads to a dramatic accumulation of fluorescent PpIX. Meanwhile, we were able to demonstrate that PpIX-fluorescence within the tumor tissue can be induced by FECH-siRNA carried by folate-coupled liposomes or dendritic polyglycerolamine nanoparticles in conjunction with a low amount of 5-ALA. PpIX-based fluorescence is excited only if the siRNA hits its target, FECH mRNA, within the cytosol. Hence, this method allows an evaluation of siRNA delivery by the detection of the newly formed PpIX-based fluorescence e.g. by flow cytometry. Due to the omnipresence of the heme-synthesis pathway, targeted application of siRNA may provide a general means for cellular imaging and determination of the successful delivery of siRNA.This approach exhibits no relevant toxicity, because siRNA-silencing of FECH leads to an endogenous and non-toxic fluorescence by affecting the cellular heme metabolism. Specific advantages of this reporter system are the positive readout of siRNA delivery, no need for transfection of a reporter gene and no need for long and complex procedures involving transcription, translation, and posttranslational modifications of the reporter molecule itself. Carriers that are able to transport FECH siRNA in a highly efficient manner may also be suitable for other siRNA-based probes.Thus, this novel reporter systemenables the selection and optimization of carriers for siRNA transport and transfection of the target tissue.

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MicroRNAs involve inhibition of tumor progression by NSAIDs

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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 45 publications in many prestigious journals and is serving as the member of editorial board and *ad-hoc* reviewer for many journals and grant agencies.