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Functional impairment of microRNAs induced by chronic inflammation is the cause of inflammation-associated colon tumorigenesis

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Abstract

Background: A widespread downregulation of microRNAs is commonly observed in human cancers and is involved in cellular transformation and tumorigenesis. Because we previously reported that microRNA functions are inhibited under various kinds of cellular stresses including inflammatory cytokines in vitro, we hypothesized that chronic inflammation in vivo may also cause chronic functional impairment of microRNAs, which mimics a global reduction of microRNA abundance, resulting in a causal role in inflammation-associated tumorigenesis. **Methods & Results: 1)** To examine this hypothesis, we first confirmed the functional impairment of microRNAs under inflammatory stimuli in vitro using artificial reporter constructs. The derepression of microRNA-targeting reporter activities by inflammatory stimuli could also be observed using reporter constructs containing natural 3'UTR sequences of c-myc and Lin28B genes, which are targeted by endogenous let-7. **2)** Next, we constructed reporter transgenic mice bearing CMV-promoter driven GFP construct carrying target sequences of microRNAs in its 3'UTR, and monitored the changes of microRNA functions in vivo during the course of a Dextran Sulfate Sodium (DSS) induced colitis-associated colon tumor model. The expression levels of GFP were significantly increased during colitis, suggesting that microRNA functions were impaired during the chronic inflammation in vivo. The expression levels of microRNA-target oncogenes such as c-myc and Lin28B in the colonic mucosa were indeed upregulated. **3)** Lastly, to determine the consequences of the global functional impairment of microRNAs during the colitis, we examined Dicer-deficient mice, which have globally low levels of microRNA expression and may mimic the functional impairment of global microRNAs induced by chronic inflammation described above. As expected, Dicer deficient mice were more liable to have the colitis-associated tumors. This indicates that the global decrease of

microRNAs leads to oncogenesis, suggesting that the functional impairment of global miRNAs during chronic inflammation can also be a cause of the inflammation-associated carcinogenesis. **Conclusion:** In conclusion, we propose a novel concept that the attenuation of global microRNA functions by chronic inflammation is the cause of inflammation-associated tumorigenesis.