Does miRNA-155 Promote Cyclooxygenase-2 Expression in Cancer?

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Abstract

MicroRNA (miR)-155 and cyclooxygenase (COX)-2 are both elevated in numerous cancers including colorectal cancer. MiR-155 enhances COX-2 expression and is an established regulator of epithelial-mesenchymal transition and inflammation. Inhibition of miR-155 or COX-2 exhibit similar negative effects on tumorigenicity. Thus, it is hypothesized that miR-155 may be a promising target for antagonizing COX-2 expression in colorectal and other cancers.

Introduction

Nonsteroidal anti-inflammatory drugs enhance cancer survival rates by promoting tumor regression in animal models and human studies of colon cancer [Wang et al., 2005]. They function, in part, by inhibiting cyclooxygenase (COX) production of the eicosanoid precursor, prostaglandin H2. COX enzymes exist in two isoforms encoded on two distinct genes, COX-1 (PTGS1) and COX-2 (PTGS2), although a splice variant encoded by PTGS1, termed COX-3 has been reported [Shaftel et al., 2003]. COX-1 is constitutively expressed in most cells while COX-2 is typically not expressed under physiological conditions. COX-2 expression is induced by a variety of extracellular stimuli including cytokines, chemokines, and growth factors.

COX-2 in Cancer

COX-2 exhibits elevated expression in colorectal cancer [Eberhart et al., 1994; Sano et al., 1995]. Clinical studies demonstrate that COX-2 inhibition greatly reduces the risk of colorectal cancer [Smallley and DuBois, 1997]. In addition, COX-2 is expressed at high levels in breast cancer and lung cancer [Parrett et al., 1997; Wolff et al., 1998]. These studies indicate that dysregulation of COX-2 gene expression may
exist in colorectal and other cancers. Recently, investigations into COX-2 dysregulation in colorectal
cancer have focused on post-transcriptional regulation.

In colorectal cancer, dysregulation of COX-2 post-transcriptional regulation by AU-rich element binding
proteins and miRNAs is well documented [Young and Dixon, 2010; Dixon et al., 2013]. MicroRNAs
(miRNAs) are dysregulated in numerous diseases including cancer. Validated human miRNAs that target
COX-2 for miRNA-mediated repression include miR-146a/b [Sato et al., 2010; Comer et al., 2014], miR-
16 [Young et al., 2012], miR-143 [Kim et al., 2011], miR-199a-3p [Akhtar and Haqqi, 2012], miR-26a [Ji
et al., 2010], and miR-101a [Tanaka et al., 2009]. Thus, a number of miRNAs have been validated as
post-transcriptional regulators of COX-2. miR-155 expression positively correlates with COX-2
expression in cancer and is elevated in numerous cancers including colorectal cancer, lymphomas, breast
cancer, and lung cancer [Kluiver et al., 2005; Volinia et al., 2006; Wang et al., 2012]. miR-155 is encoded
by the oncogenic BIC gene [Eis et al., 2005]. An extensive review of miR-155 function in cancer is
beyond the scope of this mini-review, thus the readers are referred to Chen et al. [2014].

In brief, miR-155 is a p53 regulated, transforming growth factor-β, and pro-inflammatory mediator-
induced miRNA that promotes epithelial-mesenchymal transition by regulating numerous genes including
Ras homolog gene family member A and CCAAT/enhancer-binding protein-β [Kong et al., 2008;
Johansson et al., 2013; Basova et al., 2014]. miR-155 has been extensively studied in the immunology
field, as it is a major regulator of the immune response [Vigorito et al., 2013]. miR-155 enhances COX-2
gene expression in human airway smooth muscle cells [Comer et al., 2015]. In addition, miR-155
enhances expression of COX-2 in murine macrophages [Lee et al., 2011]. The mechanism responsible for
miR-155 enhancement of COX-2 has not been determined, but it may involve miR-155-mediated
repression of suppressor of cytokine signaling-1 or phosphatidylinositol-3,4,5-triphosphate 5 phosphatase
(SHIP1) [O'Connell et al., 2009; Jiang et al., 2010]. Repression of SHIP1 may lead to enhancement of
mRNA stability in an Akt dependent manner [Sheng et al., 2001]. Akt-dependent stabilization of mRNA
was proposed for enhancement of CXCL8 expression by miR-155 in IB3-1 cells in a process that may
involve Akt regulation of RNA binding proteins [Schmidlin et al., 2004; Gherzi et al., 2006; Bhattacharyya et al., 2011]. Akt activity is elevated in numerous cancers and inhibition of Akt signaling in TMK-1 and MKN-28 gastric cancer cells reduced COX-2 expression [Thiel et al., 2006]. miR-155 function has been investigated in numerous cancer cell lines. Knockdown of miR-155 in OCI-Ly3 cells reduced Akt activity [Huang et al., 2012]. In HT29 [Pu et al., 2012] and A549 [Zang et al., 2012] cells inhibition of miR-155 function reduced cell proliferation and increased cell sensitivity to cisplatin-induced apoptosis. In MDA-MB-157 cells, inhibition of miR-155 induced apoptosis and reduced cell proliferation [Zheng et al., 2013]. Taken together, these studies indicate that miR-155 may regulate Akt signaling, proliferation, apoptosis, and chemoresistance in cancer. Furthermore, as miR-155 is elevated in cancers that exhibit elevated COX-2, it is plausible to hypothesize that miR-155 may be responsible, in part, for enhancing the expression of COX-2 in these cancers, even though miR-155 does not directly target human COX-2 mRNA.

In support of this hypothesis, the effects observed with miR-155 inhibitors are similar to effects observed for COX-2 inhibition in cancer cell lines [Hu et al., 2003; Saikawa et al., 2004]. A reduction in COX-2 expression would reduce COX-2 derived eicosanoid production and these eicosanoids have been shown to promote cancer cell proliferation, migration, apoptosis, and invasion in different studies [Wang and Dubois, 2010]. Thus, a miR-155 inhibitor may be beneficial in colorectal and other cancers.

Abundant evidence demonstrates that the expression of COX-2 and miR-155 positively correlate in colorectal and other cancers. COX-2 expression is thought to be partly responsible for the tumorigenesis of colorectal cancer and miR-155 functional studies indicate that miR-155 inhibition reduces the tumorigenicity of various cancer cell lines. The mechanism responsible for miR-155 enhancement of COX-2 expression has not been identified yet, but miR-155 regulation of Akt signaling is a candidate pathway. As such, studies investigating miR-155 regulation of COX-2 expression in colorectal and other cancers are warranted. Such studies may reveal novel mechanisms responsible for COX-2 elevation and
promotion of tumorigenesis in these cancers and may lead to the development of novel RNA interference-based drugs for treating these cancers.
References


