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 [Smalley 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

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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

Akhtar N, Haqqi TM. 2012. MicroRNA-199a* regulates the expression of cyclooxygenase-2 in human chondrocytes. Ann Rheum Dis 71:1073–1080.

Basova P, Pospisil V, Savvulidi F, Burda P, Vargova K, Stanek L, Dluhosova M, Kuzmova E, Jonasova A, Steidl U, et al. 2014. Aggressive acute myeloid leukemia in PU.1/p53 double-mutant mice. Oncogene 33:4735–4745.

Bhattacharyya S, Balakathiresan NS, Dalgard C, Gutti U, Armistead D, Jozwik C, Srivastava M, Pollard HB, Biswas R. 2011. Elevated miR-155 promotes inflammation in cystic fibrosis by driving hyperexpression of interleukin-8. J Biol Chem 286:11604–11615.

Chen Z, Ma T, Huang C, Hu T, Li J. 2014. The pivotal role of microRNA-155 in the control of cancer. J Cell Physiol 229:545–550.

Comer B, Camoretti-Mercado B, Kogut P, Halayko A, Solway J, Gerthoffer W. 2015. Cyclooxygenase-2 and microRNA-155 expression are elevated in asthmatic airway smooth muscle cells. Am J Respir Cell Mol Biol 52:438–447.

Comer BS, Camoretti-Mercado B, Kogut PC, Halayko AJ, Solway J, Gerthoffer WT. 2014. MicroRNA-146a and microRNA-146b expression and anti-inflammatory function in human airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 307:L727–734.

Dixon DA, Blanco FF, Bruno A, Patrignani P. 2013. Mechanistic aspects of COX-2 expression in colorectal neoplasia. Recent Results Cancer Res 191:7–37.

Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. 1994. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 107:1183–1188.

Eis P, Tam W, Sun L, Chadburn A, Li Z, Gomez M, Lund E, Dahlberg J. 2005. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc Natl Acad Sci USA 102:3627–3632.

Gherzi R, Trabucchi M, Ponassi M, Ruggiero T, Corte G, Moroni C, Chen C-Y, Khabar KS, Andersen JS, Briata P. 2006. The RNA-binding protein KSRP promotes decay of beta-catenin mRNA and is inactivated by PI3K-AKT signaling. PLoS Biol 5:e5.

Hu K, Yu C, Mineyama Y, McCracken J, Hillebrand D, Hasan M. 2003. Inhibited proliferation of cyclooxygenase-2 expressing human hepatoma cells by NS-398, a selective COX-2 inhibitor. Int J Oncol 22:757–763.

Huang X, Shen Y, Liu M, Bi C, Jiang C, Iqbal J, McKeithan TW, Chan WC, Ding SJ, Fu K. 2012. Quantitative proteomics reveals that miR-155 regulates the PI3K-AKT pathway in diffuse large B-cell lymphoma. Am J Pathol 181:26–33.

Jiang S, Zhang H-W, Lu M-H, He X-H, Li Y, Gu H, Liu M-F, Wang E-D. 2010. MicroRNA-155 functions as an OncomiR in breast cancer by targeting the suppressor of cytokine signaling 1 gene. Cancer Res 70:3119–3127.

Ji Y, He Y, Liu L, Chong X, Zhong X. 2010. MiRNA-26b regulates the expression of cyclooxygenase-2 in desferrioxamine-treated CNE cells. FEBS Lett 584:961–967.

Johansson J, Berg T, Kurzejamska E, Pang M-F, Tabor V, Jansson M, Roswall P, Pietras K, Sund M, Religa P, et al. 2013. MiR-155-mediated loss of C/EBPβ shifts the TGF-β response from growth inhibition to epithelial-mesenchymal transition, invasion and metastasis in breast cancer. Oncogene 32:5614–5624.

Kim SY, Romero R, Tarca AL, Bhatti G, Lee J, Chaiworapongsa T, Hassan SS, Kim CJ. 2011. miR-143 regulation of prostaglandin-endoperoxidase synthase 2 in the amnion: implications for human parturition at term. PloS One 6:e24131.

Kluiver J, Poppema S, de Jong D, Blokzijl T, Harms G, Jacobs S, Kroesen B, van den Berg A. 2005. BIC and miR-155 are highly expressed in Hodgkin, primary mediastinal and diffuse large B cell lymphomas. J Pathol 207:243–249.

Kong W, Yang H, He L, Zhao J, Coppola D, Dalton WS, Cheng JQ. 2008. MicroRNA-155 is regulated by the transforming growth factor beta/Smad pathway and contributes to epithelial cell plasticity by targeting RhoA. Mol Cell Biol 28:6773–6784.

Lee H, Maeng K, Dang H, Kang G, Ryou C, Jung J, Kang H, Prchal J, Yoo E, Yoon D. 2011. Anti-inflammatory effect of methyl dehydrojasmonate (J2) is mediated by the NF-κB pathway. J Mol Med (Berl) 89:83–90.

O'Connell RM, Chaudhuri AA, Rao DS, Baltimore D. 2009. Inositol phosphatase SHIP1 is a primary target of miR-155. Proc Natl Acad Sci USA 106:7113–7118.

Parrett M, Harris R, Joarder F, Ross M, Clausen K, Robertson F. 1997. Cyclooxygenase-2 gene expression in human breast cancer. Int J Oncol 10:503–507.

Pu J, Bai D, Yang X, Lu X, Xu L, Lu J. 2012. Adrenaline promotes cell proliferation and increases chemoresistance in colon cancer HT29 cells through induction of miR-155. Biochem Biophys Res Commun 428:210–215.

Saikawa Y, Sugiura T, Toriumi F, Kubota T, Suganuma K, Isshiki S, Otani Y, Kumai K, Kitajima M. 2004. Cyclooxygenase-2 gene induction causes CDDP resistance in colon cancer cell line, HCT-15. Anticancer Res 24:2723–2728.

Sano H, Kawahito Y, Wilder R, Hashiramoto A, Mukai S, Asai K, Kimura S, Kato H, Kondo M, Hla T. 1995. Expression of cyclooxygenase-1 and -2 in human colorectal cancer. Cancer Res 55:3785–3789.

Sato T, Liu X, Nelson A, Nakanishi M, Kanaji N, Wang X, Kim M, Li Y, Sun J, Michalski J, et al. 2010. Reduced miR-146a increases prostaglandin E2in chronic obstructive pulmonary disease fibroblasts. Am J Respir Crit Care Med 182:1020–1029.

Schmidlin M, Lu M, Leuenberger SA, Stoecklin G, Mallaun M, Gross B, Gherzi R, Hess D, Hemmings BA, Moroni C. 2004. The ARE-dependent mRNA-destabilizing activity of BRF1 is regulated by protein kinase B. EMBO J 23:4760–4769.

Shaftel S, Olschowka J, Hurley S, Moore A, O'Banion M. 2003. COX-3: a splice variant of cyclooxygenase-1 in mouse neural tissue and cells. Brain Res Mol Brain Res 119:213–215.

Sheng H, Shao J, Dubois RN. 2001. K-Ras-mediated increase in cyclooxygenase 2 mRNA stability involves activation of the protein kinase B1. Cancer Res 61:2670–2675.

Smalley W, DuBois R. 1997. Colorectal cancer and nonsteroidal anti-inflammatory drugs. Adv Pharmacol San Diego Calif 39:1–20.

Tanaka T, Haneda S, Imakawa K, Sakai S, Nagaoka K. 2009. A microRNA, miR-101a, controls mammary gland development by regulating cyclooxygenase-2 expression. Differ Res Biol Divers 77:181–187.

Thiel A, Heinonen M, Rintahaka J, Hallikainen T, Hemmes A, Dixon DA, Haglund C, Ristimaki A. 2006. Expression of cyclooxygenase-2 is regulated by glycogen synthase kinase-3beta in gastric cancer cells. J Biol Chem 281:4564–4569.

Vigorito E, Kohlhaas S, Lu D, Leyland R. 2013. miR-155: an ancient regulator of the immune system. Immunol Rev 253:146–157.

Volinia S, Calin G, Liu C, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, et al. 2006. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA 103:2257–2261.

Wang D, Dubois R. 2010. Eicosanoids and cancer. Nat Rev Cancer 10:181–193.

Wang D, Mann JR, DuBois RN. 2005. The role of prostaglandins and other eicosanoids in the gastrointestinal tract. Gastroenterology 128:1445–1461.

Wang M, Zhang P, Li Y, Liu G, Zhou B, Zhan L, Zhou Z, Sun X. 2012. The quantitative analysis by stem-loop real-time PCR revealed the microRNA-34a, microRNA-155 and microRNA-200c overexpression in human colorectal cancer. Med Oncol Northwood Lond Engl 29:3113–3118.

Wolff H, Saukkonen K, Anttila S, Karjalainen A, Vainio H, Ristimäki A. 1998. Expression of cyclooxygenase-2 in human lung carcinoma. Cancer Res 58:4997–5001.

Young LE, Dixon DA. 2010. Posttranscriptional regulation of cyclooxygenase 2 expression in colorectal cancer. Curr Colorectal Cancer Rep 6:60–67.

Young LE, Moore AE, Sokol L, Meisner-Kober N, Dixon DA. 2012. The mRNA stability factor HuR inhibits microRNA-16 targeting of COX-2. Mol Cancer Res 10:167–180.

Zang Y-S, Zhong Y-F, Fang Z, Li B, An J. 2012. MiR-155 inhibits the sensitivity of lung cancer cells to cisplatin via negative regulation of Apaf-1 expression. Cancer Gene Ther 19:773–778.

Zheng S, Guo G, Zhai Q, Zou Z, Zhang W. 2013. Effects of miR-155 antisense oligonucleotide on breast carcinoma cell line MDA-MB-157 and implanted tumors. Asian Pac J Cancer Prev 14:2361–2366.