of Sachs and colleagues provides fresh insight into how integrin-dependent tight binding of podocytes to the GBM regulates glomerular disease.

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Chronic inflammation has long been appreciated to play a critical role in tumor development and maintenance. Among the mechanisms involved in coordinating the initiation and resolution of inflammation are those responsible for modifying mRNA stability and/or translation. Several studies have linked the RNA-binding protein HuR, which increases mRNA stability, with malignant transformation. However, in this issue of the JCI, Yiakouvaki and colleagues compellingly demonstrate in mice that increased HuR activity in myeloid cells has a protective role in the onset of pathologic intestinal inflammation (i.e., colitis) and colitis-associated cancer (CAC). These observations highlight the need to understand the roles of HuR in distinct cell populations in vivo and suggest that enhancing HuR activity may be of clinical benefit in protecting against pathologic inflammation and cancer.

It has been clear for some time that chronic inflammation can promote and/or exacerbate tumor initiation, tumor promotion, and tumor progression (1). For example, clinical and epidemiologic studies have indicated that inflammation of the liver as a result of alcohol abuse or chronic infection with hepatitis C virus is associated with hepatocellular carcinoma; inflammation of the lung as a result of cigarette smoking, asbestos exposure, or silica exposure is associated with lung carcinoma; and inflammatory bowel diseases (IBDs) such as ulcerative colitis (UC) are associated with colon cancer. Defining the mechanisms responsible for coordinating the initiation and resolution of inflammation is therefore critical to understanding how inflammation-associated cancers arise and progress and to identifying potential therapeutic targets. Among the mechanisms responsible for coordinating the initiation and resolution of inflammation are those controlling the production and post-transcriptional regulation of mRNAs encoding inflammatory mediators. In this issue of the JCI (2), Yiakouvaki and colleagues provide a comprehensive study aimed at clarifying the role of one RNA-binding protein that controls mRNA stability and/or translation (HuR) in inflammation and inflammation-associated cancer.

Post-transcriptional regulation of gene expression by HuR

HuR is a member of the embryonic lethal, abnormal vision (ELAV) family of RNA-binding proteins that is encoded by the ELAV1 gene. It regulates gene expression via post-transcriptional mechanisms (3–5). Traditionally, HuR functions to modulate the stability and translation of target mRNAs that possess AU-rich elements (AREs) in their 3′-untranslated regions (UTRs). It has been previously demonstrated that myeloid HuR overexpression could induce translational silencing of ARE-containing transcripts, such as Tnfα, even though the mRNAs were stabilized (6). HuR is predominantly nuclear, but in response

The flip-flop HuR: part of the problem or the solution in fighting cancer?

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to various stimuli such as therapeutic agents (i.e., tamoxifen and prostaglandins), nutrient deprivation, and immune stimuli, HuR shuttles to the cytoplasm, where it acts to prolong target mRNA half-life and modulate target mRNA translation (7, 8). In vitro studies have demonstrated that HuR regulates the expression of genes involved in key cellular processes, including inflammation, tumorigenesis, the response to hypoxia, cell-cycle control, and the response to cell stress (3–5). HuR has also been demonstrated to promote cell survival by positively regulating the expression of antiapoptotic proteins and suppressing the expression of proapoptotic proteins (9–11). However, few studies have investigated the physiologic and pathologic functions of HuR in animal models, so the in vivo function of this RNA-binding protein is poorly understood. The work of Yiakouvakki and colleagues (2) provides some insight into this, specifically, HuR’s function in myeloid cells, which are pivotal regulators of inflammation.

**The role of HuR in the progression of colitis and colitis-associated cancer**

While no mutations in the gene encoding HuR have been reported in cancer, studies have suggested a link between HuR and malignant transformation (12–14). Specifically, changes in HuR levels or localization in clinical samples from patients with inflammatory disease or cancer have suggested that HuR functions in a proinflammatory and pro-tumorigenic manner (14, 15). Elevated levels of cytoplasmic HuR have been demonstrated to correlate with advanced malignancy and tumor progression for many cancers, including those of the colon (16–18). However, a number of recent studies have demonstrated that HuR might not always function in a pro-tumorigenic manner. For example, overexpression of HuR was shown to impair tumor growth in an orthotopic mouse model of estrogen receptor–negative breast cancer (19). Likewise, in a clinical correlation study of the therapeutic efficacy of the first-line chemotherapeutic agent
gemcitabine in individuals with pancreatic cancer, patients with low cytoplasmic levels of HuR exhibited a 7-fold increase in risk of mortality compared with patients with high cytoplasmic levels, suggesting that cytoplasmic HuR levels in pancreatic cancer modulate the therapeutic efficacy of gemcitabine (20). Therefore, the role of HuR in cancer remains unclear, as reports have suggested opposing roles in regard to tumor development and maintenance.

In this issue of the JCI (2), Yiakouvak and colleagues have provided compelling evidence of a protective role for HuR in chronic inflammation and tumorigenesis. To examine the role of HuR in inflammatory responses, the authors induced autosomal inactivation of the Elavl1 locus in the mouse myeloid lineage to generate mice that they termed MKO mice. In a model of LPS-induced septic shock, MKO mice were found to be more susceptible to septic shock than controls; this was true for both mice of a susceptible genetic background and those of a resistant genetic background. Interestingly, the endotoxic response of MKO mice was inversely correlated with the enhanced presence of mRNAs encoding the proinflammatory cytokines TNF, IL-6, IL-1β, and IL-12, confirming the induction of a heightened proinflammatory response. Macrophages cultured from MKO mice also revealed changes in the biosynthesis of key inflammatory mediators that could support inflammatory pathologies. Specifically, upregulation of Il6 mRNA and an accumulation of secreted IL-6 protein, a key mediator of colitis-induced cancer, were observed, as was a similar response for IL-12, which drives inflammatory Th1 responses related to systemic and intestinal inflammation.

In an effort to examine the role of HuR in organ-specific inflammation, Yiakouvak and colleagues employed a mouse model of colitis induced by DSS (2). Interestingly, MKO mice exhibited enhanced progression and maintenance of colitis (Figure 1). More striking were data obtained from experiments examining the role of myeloid HuR in a model of colitis-associated cancer (CAC) induced by dimethylhydrazine (DMH) and DSS. MKO mice exposed to DSS and DMH demonstrated increased tumor size and grading as compared with control groups. Importantly, Yiakouvak and colleagues extended these results and examined whether HuR overexpression would block colitis and CAC (2). In contrast to control groups, DSS induced only a small inflammatory response in the colons of mice in which HuR was inducibly overexpressed. Most significant, however, DSS/DMH treatment of mice overexpressing HuR in the myeloid lineage resulted in the appearance of only a few small, low-grade adenomas and reduced tumor multiplicity, as compared with control groups. These experiments highlight the protective effects of myeloid HuR activity in regulating inflammatory tumorigenesis in the mouse colon.

Therapeutic perspectives for treating pathologic inflammation and cancer
As noted above, patients with UC are at increased risk for developing colorectal cancer, and chronic inflammation is the assumed culprit. Like other solid malignancies, colitis-associated tumors are infiltrated by a variety of immune cells, including neutrophils, mast cells, natural killer cells, dendritic cells, and tumor-associated macrophages (21). Previous studies have suggested that HuR has a role in the initiation and progression of colon cancer and the associated expression of immune modulators (14, 22, 23), but now Yiakouvak and colleagues have shed new light on the inflammatory component of the process. Specifically, they provide compelling evidence that increasing HuR functions in myeloid cells is an effective strategy to combat pathologic inflammation and cancer (2).

The notion of HuR as a therapeutic target is not new; the reports linking HuR to cancer overexpression protect cancer in types other than CACs and is the protection dependent on the presence of a strong inflammatory component? More investigation into the mechanism(s) by which HuR acts to regulate inflammation and tumorigenesis as well as the potential interplay among other RNA-binding proteins would greatly add to the understanding of the in vivo function of HuR. Thus, future investigations based on the study by Yiakouvak and colleagues may provide additional therapeutic targets to combat inflammation-associated cancers.

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12. Lopez de Silanes I, Fan J, Galban CJ, Spencer RG, Becker KG, Gorospe M. Global analysis of HuR-


Epoxyeicosatrienoic acids: a double-edged sword in cardiovascular diseases and cancer

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Epoxyeicosatrienoic acids (EETs) generated from arachidonic acid by cytochrome P450 (CYP) epoxygenases have beneficial effects in certain cardiovascular and kidney diseases. Hence, great efforts have been made to develop drugs targeting the EET pathway. Some of these agents are currently under evaluation in clinical trials for treatment of hypertension and diabetes. In this issue of the *JCI*, Panigrahy et al. evaluate in a systematic way the role of CYP epoxygenases and the metabolites they generate in cancer progression. Their findings, along with previous studies, raise concerns about using these drugs in humans.

High dietary fat intake is reported to be associated with several human diseases, including diabetes and heart disease. Moreover, epidemiologic and experimental observations support the hypothesis that high dietary fat intake is also a risk factor for cancers. However, the mechanisms underlying the link between high dietary fat intake and cancer progression are poorly understood. One factor thought to be involved is arachidonic acid (AA), a major component of animal fats that is primarily found in red meats, egg yolks, and organ meats. The bioactive lipids derived from AA play critical roles in cancer progression (1). (Figure 1). Free AA can be metabolized to eicosanoids through three major pathways: the prostaglandin-endoperoxide synthase/cyclooxygenase (PTGS/COX) pathway, the lipooxygenase (LOX) pathway, and the cytochrome P450 (CYP) pathway. Prostanoids are the eicosanoids generated by the PTGS/COX pathway, while the LOX pathway generates leukotrienes and dihydroxyeicosatetraenoic acids (DHETs). The CYP enzymes that convert AA into eicosanoids include CYP epoxygenase and CYP o-hydroxylase enzymes. CYP epoxygenases, such as members of the CYP2C and CYP2J families, metabolize AA to four biologically active epoxyeicosatrienoic acids (EETs) (5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET). CYP o-hydroxylases, such as members of the CYP4A and CYP4F families, convert AA to DHETs. Among the members of the CYP2C and CYP2J families, some DHETs are converted to 11,12-EET. The CYP2C metabolites, CYP2J2, CYP2C8, and CYP2C9 are the predominant epoxygenase isoforms that convert AA into EETs. All EETs are then further metabolized to less active dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH).

EET signaling in cardiovascular and kidney diseases

EETs are produced primarily by endothelial cells, although they are also produced by other cell types, such as astrocytes and cardiomyocytes. Because EETs induce vasodilation and exert antiinflammatory effects in blood vessels in an autocrine manner (2), they can lower blood pressure, protect the myocardium and brain from ischemia, attenuate hypertension-induced renal damage, and reduce cigarette smoke-induced lung inflammation (3). Increasing evidence reveals that EETs govern these various biological functions by inducing endothelial cell proliferation, survival, and tube formation and stimulating renal epithelial cell proliferation and survival through multiple signaling pathways (4). Hence, great efforts have been made to develop drugs targeting these pathways. For example, 11,12-EET has been shown to improve coronary artery endothelial function when it is added to transplant preservation solutions (5). Moreover, an sEH inhibitor (AR9281) is currently under evaluation in phase II clinical trials as a treatment for patients with hypertension and type 2 diabetes on the basis of evidence that sEH inhibitors have beneficial effects in animal models of hypertension and cardiovascular diseases (3, 6). However, emerging evidence shows that EETs can promote cancer progression by directly promoting cancer cell proliferation, survival, migration, and invasion. In this issue of the *JCI,*...