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Commentary

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miR-122 regulates hepatic lipid metabolism and tumor suppression

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In this issue of *JCI*, two independent groups describe the effects of germline and liver-specific deletion of *Mir122a*, the predominant liver miRNA. Their findings reveal a critical role for miR-122 in fat and cholesterol metabolism but suggest that other metabolic actions of the liver are independent of miR-122. Knockout mice also displayed hepatic inflammation, fibrosis, and a high incidence of hepatocellular carcinoma, suggesting that miR-122 has a tumor suppressor role in hepatocytes.

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate the expression of complementary messenger RNAs. Since their initial discovery in 1993 in *Caenorhabditis elegans*, more than 1,400 miRNAs have been detected in the human transcriptome. In addition to regulating physiologic processes, miRNAs have also been implicated in numerous disease states. The broad function of miRNA in the liver was investigated by studying mice with conditional deletion of *Dicer1* in hepatocytes (1, 2). Despite the lack of mature miRNA in this model, the liver was able to perform the essential functions of blood glucose regulation, albumin production, and bilirubin metabolism. However, over time, it became clear that miRNA plays an important role

in fat metabolism, inflammation, and cell cycle regulation in the liver, as these animals developed progressive hepatic steatosis, hepatitis, apoptosis, and hepatocellular carcinoma (HCC) (1, 2).

miR-122 is the predominant liver miRNA, making up 70% of the total miRNA population (3). The activity of miR-122 has previously been assessed through antisense oligonucleotide-mediated knockdown, implicating miR-122 in cholesterol and fat metabolism (4, 5). Although HCC was not observed in the time frame of these studies, several groups have reported tumor suppressor activity for miR-122, based on decreased miR-122 levels in tumor tissue and inhibitory effects of miR-122 in tumorigenicity assays (6). However, knockdown experiments are limited by their transient nature and the potential for off-target effects.

In this issue of *JCI*, Hsu et al. and Tsai et al. present definitive evidence of miR-122

function using genetic deletion in mice (7, 8). Mice with germline or conditional deletion of *Mir122a* in the liver were viable and fertile. However, as the animals aged, they developed steatohepatitis, liver fibrosis, and HCC. These groups define direct roles for miR-122 in both fat metabolism and tumor suppression, although it is less clear whether the link to fibrosis is directly or indirectly related to miR-122 loss. Thus, although miR-122 cannot be construed as a “master regulator” of liver function — as the mutant mice have generally normal liver function — it is a critical checkpoint both in hepatic fat production and hepatocellular proliferation (Figure 1).

miR-122 regulates fat and cholesterol metabolism

Temporary miR-122 inhibition has been shown to reduce serum cholesterol via downregulation of genes involved in cholesterol biosynthesis such as HMG-CoA reductase (4). This is recapitulated in the genetic models: the serum lipid profiles of both liver-specific knockouts (LKO) and germline knockouts (KO) show a 30% reduction in total cholesterol, LDL, HDL, and serum triglyceride (TG). However, the livers of both KO and LKO mice also have progressive steatohepatitis (7, 8), a feature

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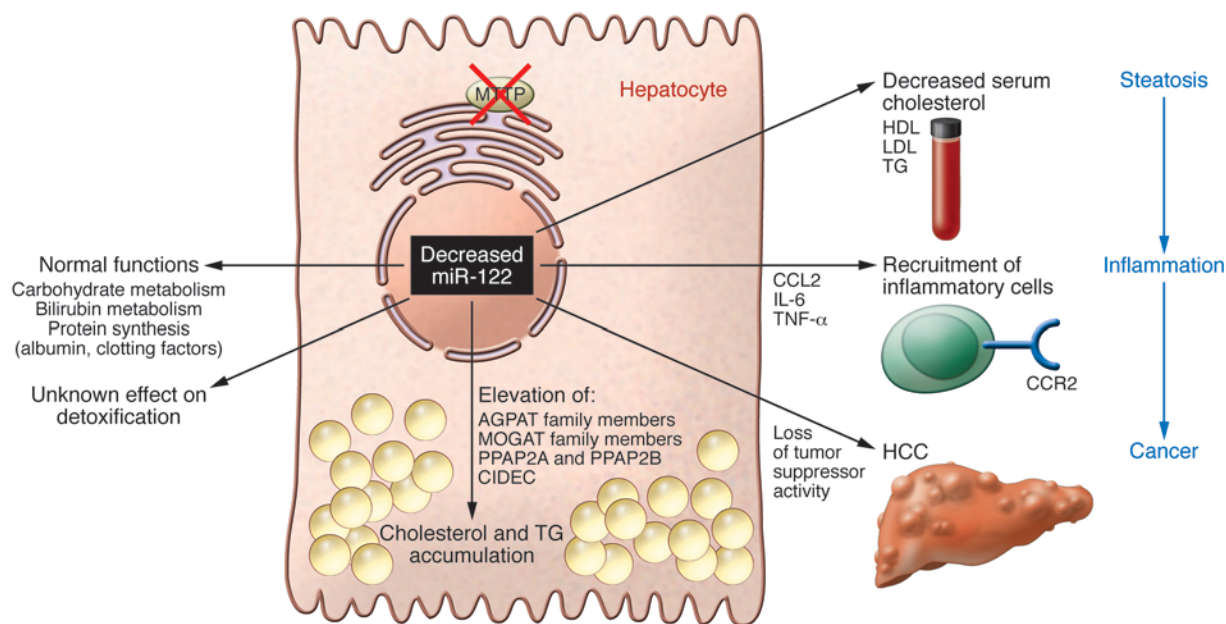


Figure 1
 Overview of the consequences of miR-122 loss on hepatocyte function. The normal functions of the hepatocyte include carbohydrate and lipid metabolism, bilirubin excretion, and detoxification of endogenous compounds and xenobiotics. In this issue, Tsai et al. and Hsu et al. demonstrate that loss of miR-122 results in increased lipid synthesis and decreased lipid export, but other hepatocyte functions are unaltered. Loss of miR-122 also led to increased inflammation and fibrosis, and eventually the development of HCC, suggesting the miR-122 plays a tumor-suppressive role.

not seen in the previous knockdown studies (4, 5). The concordance of phenotypes in the KO and LKO mice is as expected, given the lack of miR-122 expression in non-hepatic tissues.

Hsu and colleagues identified the mechanism of steatosis in the mutants by performing gene expression profiling of *Mir122a*-LKO hepatocytes (7). They noted upregulation of genes known to be involved in lipid synthesis in the liver, including *Agpat1*, *Mogat1*, *Agpat3*, *Agpat9*, *Ppap2a*, *Ppap2c*, which are part of the TG biosynthesis pathway (9). Additionally, there was upregulation of *Cidec*, also known as FSP27, which is a protein that localizes to lipid droplets, negatively regulates lipolysis, and enhances TG accumulation. Consistent with the gene expression changes, the mutant livers synthesize more TG than controls but secrete less, resulting in TG accumulation in hepatocytes. The authors used reporter assays to confirm that *Agpat1* and *Cidec* are direct miR-122 targets.

In their analysis of the fatty liver phenotype, Tsai and colleagues focused on MTTP (microsomal TG transfer protein) and found its expression level to be reduced in the *Mir122a*-KO mice (8). MTTP normally functions by enhancing the rate of lipid transfer between vesicles and is necessary for

the assembly of lipoproteins (10). When *Mtpp* expression was restored, serum cholesterol and fasting TG levels normalized. This surprising result suggests that either the lipid phenotype of the KO mice is primarily due to effects on *Mtpp* expression or that overexpression of *Mtpp* has a dominant effect on hepatic steatosis. The authors note that *Mtpp* is not predicted to be a direct target of miR-122; this makes sense in light of the parallel loss of *Mtpp* in mice lacking the repressive activity of miR-122. While Hsu and colleagues do not present any data regarding *Mtpp*, it is noteworthy that they did detect a decrease in the expression of another microsomal lipid transporter, *Stard4* (7).

Based on these reports, miR-122 appears to play an important role in cholesterol and TG metabolism within the liver by directly or indirectly regulating cholesterol and TG biosynthesis and excretion. They make it clear that a decrease in circulating TG is not beneficial if the underlying reason is excessive retention of TG within hepatocytes. Likewise, the decrease in serum lipoproteins is of interest from the cardiovascular standpoint, although both the LDL and the HDL fractions were depressed; it will be important for future studies to determine the effect miR-122 loss in the context of atherosclerosis.

miR-122 loss results in hepatic inflammation and fibrosis

Mir122a-KO animals develop steatohepatitis and liver fibrosis (7, 8), phenotypes that were not observed in prior studies using antisense oligonucleotide-mediated *Mir122a* knockdown. Both groups also demonstrated an increase in infiltrating inflammatory cells in miR-122-deficient liver (7, 8). The infiltrating cells were CD11b^{hi}Gr1⁺, a population of immature myeloid cells with monocyte and granulocyte morphology. They produce high levels of IL-6 and TNF- α , and these cells are known to promote fibrosis in the injured liver (11).

Is inflammation directly regulated by miR-122, or is the phenotype an indirect result of chronic steatosis? The experiment employing exogenous restoration of *Mtpp* expression implies the latter, because resolution of steatosis by *Mtpp* also led to reduced inflammation and fibrosis. On the other hand, the authors used reporter assays to show that the chemokine gene *Ccl2* is a direct miR-122 target gene in Hepa cells, albeit only to a mild degree (8).

The *Mtpp* rescue experiment also implies that miR-122 regulates hepatic fibrosis indirectly. However, *Klf6* was identified as a miR-122 target gene in reporter assays,



and the suppression of *Klf6* by shRNA led to a reduction in TGF- β 1 expression and collagen deposition in the KO mice (8). Nevertheless, the reporter assays revealed a less than 2-fold effect of miR-122 on *Ccl2* and *Klf6* expression. Finally, the reduction in fibrosis observed following treatment with *Klf6* shRNA may be completely independent of miR-122 function, because *KLF6* is also expressed in activated hepatic stellate cells (which lack miR-122), where it regulates many fibrosis genes (12). Thus, the most likely sequence of events in these models is that steatosis is caused by direct effects of miR-122 deficiency, and that inflammation and fibrosis follow, with minor effects due to de-repression of *Ccl2* and *Klf6* in hepatocytes.

miR-122 is a hepatic tumor suppressor

miR-122 levels are reduced in experimental models and human samples of HCC, and loss of miR-122 is associated with tumor invasiveness and cancer progression (13–15). Therefore, it has been speculated that this miR acts as a tumor suppressor. In the models described by Tsai et al. and Hsu et al., HCC develops in both the KO and LKO mice. In the germline knockout, the incidence is 50% at 1 year of age. Both groups noted a striking sex disparity in the occurrence of HCC in miR-122-deficient mice, with a male to female ratio of approximately 4:1 in the LKO mice (7) and the KO mice (8). Hsu and colleagues did not observe a sex bias in the KO mice they analyzed, but in light of both studies, this may reflect random variation from male predominance. The males also have greater tumor burden and more advanced tumor grade than the females. Both of these features are similar to those observed in human HCC (16). In the mouse model, the sex disparity may be due in part to increased IL-6 levels in the males, illustrating the complex relationship among sex hormones, inflammation, and tumor suppressors/oncogenes in HCC.

To further understand the involvement of miR-122 in carcinogenesis, Hsu et al. made use of an HCC experimental model wherein transgenic mice harbor both a tetracycline-repressible *MYC* gene and a liver activator promoter-driven tet-transactivator protein, resulting in hepatic tumors in the absence of liver damage or inflammation. Interestingly, miR-122 levels are strongly reduced in this model. Remark-

ably, administration of a recombinant adeno-associated viral vector expressing *MIR122* (after the establishment of small tumors) resulted in a reduction in tumor burden from 40% to 7.7% of liver mass. Thus, miR-122 appears to act as a tumor suppressor in a manner that is independent of its roles in fat metabolism or inflammation. It likely mediates this effect via a variety of target genes that are important in cell cycle regulation and hepatocyte differentiation, such as the stem cell genes *Prom1*, *Thy1*, and *Epcam*. To further support a direct tumor suppressor function for miR-122, it would be interesting to determine whether the restoration of *Mtpp* also prevents HCC in the KO mice, a question not addressed by Tsai and colleagues (8). Finally, miR-122 loss may also promote epithelial-mesenchymal transition, as E-cadherin mRNA levels were reduced in the mutant livers even before the appearance of HCC.

Other functions of miR-122

A recent study has linked miR-122 to liver development through a positive feedback loop with the *Onecut* hepatocyte transcription factor gene family (17). Mouse embryos lacking both *Onecut1* (*Hnf6*) and *Onecut2* have reduced hepatic miR-122 levels, and *Onecut1* can bind and activate the *Mir122a* locus. Transgenic mice overexpressing miR-122 in the developing liver have elevated *Onecut1* levels and subtle defects in hepatocyte and cholangiocyte differentiation. However, loss-of-function analysis in this study was restricted to morpholino-based knockdown in zebrafish, with the analysis limited to early time points. In this respect, the *Mir122a*-KO mouse has the potential to confirm a developmental function for miR-122. Hsu et al. noted that liver histology was normal at birth and that *Onecut1* expression was not altered in adult LKO or KO mice. Although not described in either of the articles, it will be revealing to analyze *Onecut1* levels and liver cell differentiation at embryonic time points in the mutant mice; based on the *Mir122a*-transgenic mouse (17), there may be defects in liver cell differentiation or developmental timing.

miR-122 also has a compelling function in HCV replication. It is required for viral replication and interacts with HCV RNA, although it is not required for HCV RNA synthesis (18–21). Although miR-122 levels have not been directly correlated with viral

load in liver samples from patients infected with HCV (22), in non-human primates, treatment with a miR-122 inhibitor results in a significant decrease in HCV viral load, and it is being investigated as a potential therapeutic for HCV (23). The two miR-122 studies in this issue of the *JCI* suggest that the use of this miR as anti-HCV therapy will need to be balanced with the potential for developing HCC, especially since patients with chronic HCV already have an increased risk for HCC. Furthermore, patients with hepatitis C have increased risk for cardiovascular disease and insulin resistance, so the effects of miR-122 inhibition on cardiovascular health will also need to be considered.

As a whole, the findings reported by Hsu et al. and Tsai et al. definitively describe the phenotype of miR-122 loss in the quiescent liver. miR-122 is a key regulator of multiple hepatic pathways, as highlighted by its direct roles in fat metabolism, tumor suppression, and perhaps inflammation and fibrosis. Despite this, liver development and hepatocyte differentiation occur normally in mice lacking miR-122. miR-122-deficient livers also continue to perform bilirubin, protein, glucose, and xenobiotic metabolism. In future studies, it will be intriguing to see whether these other functions are dependent on miR-122 in the context of stress, such as a high-fat diet or hepatotoxins. Conversely, while loss of miR-122 causes steatohepatitis, it is unknown whether exogenous miR-122 can ameliorate fatty liver disease caused by diet or toxins. Finally, the tumor-suppressive function of miR-122 illustrated by both groups suggests that the restoration of miR-122 expression may be of benefit in HCC – but as with many other tumor suppressor miRNAs, delivery of the miRNA remains a major challenge.

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How many neutrophils are enough (redux, redux)?

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Many chemotherapeutic regimens produce neutropenia, which predisposes to microbial infection. However, not all neutropenic individuals develop infections, so the ability to predict this outcome would be a powerful clinical tool. In this issue of the JCI, Malka et al. describe a dynamic system model of neutrophil bactericidal activity that confirms and extends the concept of critical neutrophil concentration. The authors demonstrate that when the neutrophil concentration approaches the critical concentration, bacterial populations in contact with them exhibit bistability. Their experimental findings raise the intriguing possibility of greater variability in bactericidal activity of neutrophils from healthy adults than heretofore recognized; their model predicts that this could have life-and-death consequences.

Although the link between neutropenia and infection risk is clear, the precise number of neutrophils required to maintain health remains a topic of intense research interest. Neutrophils continuously patrol the luminal surfaces of endothelial cells, searching for signs of infection or inflammation. Such signs stimulate them to emigrate from blood into extravascular compartments (1). There, their armamen-

tarium of chemoattractant and phagocytosis-promoting plasma membrane opsonin and pattern-recognition receptors enable them to phagocytose approximately 40–50 bacteria/neutrophil (2), and their preformed granule proteins and capacity to produce high intravacuolar concentrations of reactive oxygen species (3) enable them to kill their bacterial prey. The extracellular release of DNA-histone antimicrobial protein-containing nets (4) that entrap bacteria and kill yeast/fungi (5) extends their bactericidal and fungicidal activities into their afterlives and further enhances their efficacy as guardians of tissue sterility.

Chemotherapeutic agents that inhibit neutrophil biogenesis (6–8) and/or reduce their bactericidal activity (7) produce neutropenia (i.e., <500,000 neutrophils/ml blood). Although neutropenia predisposes to infection, it has little direct effect on the sterility of blood because under most (9) — but not all (10) — conditions, hepatic and splenic macrophages are the cells primarily responsible for clearing bacteria from the circulation. Indeed, as suggested by Crosby (11) and supported by the studies of Wright et al. (12) and Koene et al. (13), it is the tissue neutrophil concentration (N) that determines whether the small number of bacteria that breach mucosal surfaces each day will find fertile soil for growth, or be engulfed and killed. Thus, while a blood N value of 5×10^5 neutrophils/ml is a call for vigilance, it is an imprecise measure of the likelihood of infection. This is so because blood is primarily the conduit by which neutrophils travel from bone marrow to tissues, and the blood N reflects the sum of the rates at which neutrophils are produced and released from bone marrow into the circulation, and the rates at which they are consumed in tissues (14) and/or recycled to spleen and bone marrow for destruction (15).

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