Overall, these two articles independently demonstrate an important susceptibility of tumor cells to caloric restriction and to separate mechanisms by which this leads to an enhancement of immune-mediated cell death. Both demonstrate that targeting tumor metabolism can alter the tumor microenvironment in a way that favors effector (versus suppressor) immune responses. However, both manuscripts leave open-ended whether or not these therapies can be utilized to enhance checkpoint inhibition or other immune-mediated therapies in development. In addition, the specific effect of these therapies on the T cell function and differentiation remains to be determined. While the authors provide some insight and demonstrate how caloric restriction leads to favorable changes in the populations of immune cells, future investigations will need to look at the impact on their function. In fact, in contrast to these studies, previous investigations in a mouse model of lupus demonstrated that fasting actually led to an expansion of T-regulatory cells (Liu et al., 2012). Understanding how caloric restriction leads to differing phenotypes in benign and malignant disease might provide additional insight into future therapeutic targets. In summary, these findings suggest a potentially safe and novel approach to enhancing immunotherapies, but future studies investigating the impact of caloric restriction on T cell function and in combination with other immunotherapies will be important in determining what clinical impact these might have in oncology.

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P(URI)fying Novel Drivers of NASH and HCC: A Feedforward Loop of IL17A via White Adipose Tissue

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How obesity and metabolic syndrome trigger non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) remains elusive. In this issue, Gomes and colleagues describe that nutrient surplus induces hepatic URI expression, triggering genotoxicity and IL17A expression, thus leading to insulin resistance, NASH, and HCC. IL17A signaling blockers might become a readily translatable therapy.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the second most common cause for cancer-related death. Chronic hepatitis and liver damage, upon which fibrosis, cirrhosis, and HCC develop, are mainly caused by hepatitis virus (HBV; HCV) infections, chronic alcohol abuse, or high caloric intake combined with a sedentary lifestyle (Llovet et al., 2015; Margini and Dufour, 2016; Singal and El-Serag, 2015). The latter causes overweight and metabolic syndrome, currently reaching pandemic dimensions in industrialized and developing countries (Margini and Dufour, 2016). Non-alcoholic fatty liver disease (NAFLD) is a frequent manifestation of overweight and metabolic syndrome, and a significant proportion of NAFLD patients develop non-alcoholic steatohepatitis (NASH) (Margini and Dufour, 2016). NASH-driven HCC is one of the most rapidly increasing cancers in the USA and Europe. However, curative or efficient therapies are lacking (Llovet et al., 2015). Although the sequence from NAFLD to NASH to fibrosis/cirrhosis to HCC is known, the underlying mechanisms of transition from one disease stage to another and the interconnection

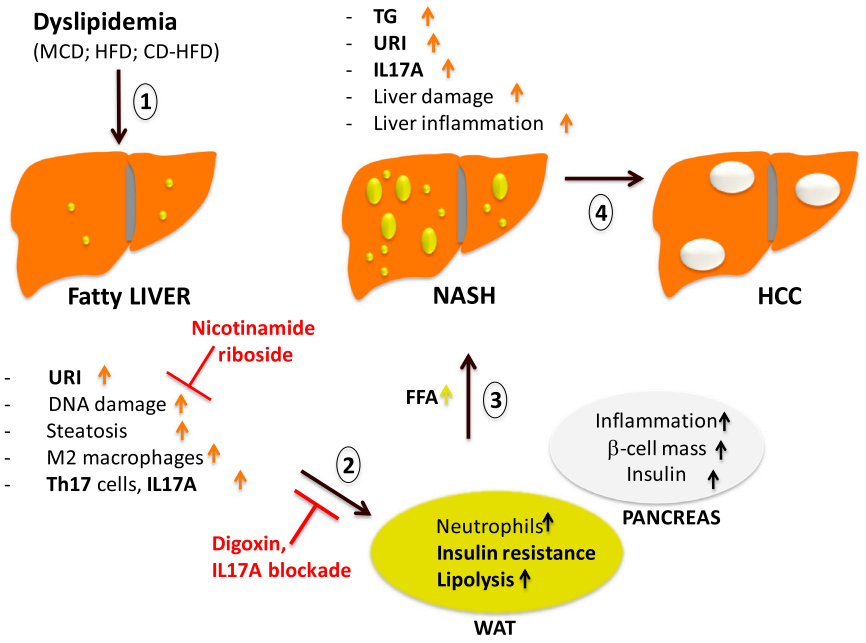

Figure 1. Role of URI-Driven IL17A in the Crosstalk between Fatty-Liver and WAT-Driving NASH and HCC

(1) Upon systemic dyslipidemia, URI expression is induced in the liver. This causes genotoxic stress, lipid deposition, liver damage, and inflammation, characterized by an increase and activation of Kupffer cells, Th17 cells (intrahepatic and circulating), and IL17A upregulation. (2) IL17A recruits neutrophils in WAT, causing increased lipolysis, IR and FFA release, and pancreatic inflammation. (3) FFA release induces hepatic TG accumulation, driving NASH and further inflammation (e.g., including IL17A induction), which, in a feedforward loop, increases URI. (4) Persistence of this feedforward loop causes HCC. Nicotinamide riboside, digoxin, and IL17A block (red) greatly reduce NASH and HCC development.

between the liver and other metabolic organs during pathogenesis are unclear. Recent studies show that $CD8^+$, NKT cells, endoplasmic reticulum (ER) stress, and TNF/IL6-dependent signaling cascades drive NASH and HCC (Nakagawa et al., 2014; Park et al., 2010; Wolf et al., 2014). However, the precise mechanisms causing obesity-triggered genotoxicity in the liver, NASH, and subsequent HCC development remained unclear.

In this issue of *Cancer Cell*, Gomes and colleagues link nutrient excess with hepatic URI overexpression and genotoxicity, inducing an intrahepatic, white adipose tissue (WAT)-related inflammation, forcing a feedforward loop of IL17A-driven WAT insulin resistance (IR), NASH, and HCC (Gomes et al., 2016) (Figure 1). URI—an "addicting" oncogene (Theurillat et al., 2011)—is modulated by viral infections and inflammation causing HCC (Tummala et al., 2014). Notably, different diets inducing NASH (methionine/choline-deficient [MCD]) or NASH/HCC (choline-deficient/high-fat diet [CD-HFD]) triggered hepatic URI expression, whereas starvation reduced hepatic URI expression (Gomes et al., 2016). Thus, URI might link caloric surpluses to NASH. Intriguingly, mice hemizygous for hepatic URI ($URI(+/\Delta)^{hep}$) under HFD, MCD, or CD-HFD deposited less-hepatic lipids, despite similar body and liver weight compared to controls, suggesting a role of URI in NAFLD. In mice expressing inducible human URI in liver ($hURI\text{-}tetOFF^{hep}$), steatohepatitis developed even upon low-chow diet, which was abrogated when human URI expression was dampened from the age of 8 weeks, indicating that URI expression sustains steatohepatitis. How URI-dependent DNA damage and IL17A induction occurs during steatosis, what genomic alterations are generated, and whether persistent DNA damage by URI at later stages of NASH significantly contributes to hepatocarcinogenesis will be important to investigate in the future.

The authors show that URI is also responsible for chronic liver injury contributing to steatohepatitis. Using $hURI\text{-}tetOFF^{hep}$ and $URI(+/\Delta)^{hep}$ mice, the authors demonstrated that hepatic steatosis is caused by fatty acid (FFA) uptake rather than de novo synthesis (Figure 1). Next, the authors asked whether increased liver triglycerides originated from IR-mediated WAT lipolysis. Indeed, $hURI\text{-}tetOFF^{hep}$ mice displayed less body fat, whereas lack of hURI expression prevented fat loss. In addition, impaired glucose tolerance and insulin sensitivity depended on hURI expression, indicating that WAT IR required sustained hepatic URI expression. Thus, WAT IR triggers lipolysis and FFA release into serum, possibly causing steatohepatitis in $hURI\text{-}tetOFF^{hep}$ mice.

Accordingly, neutrophil infiltration—known to contribute to WAT IR—was found in $hURI\text{-}tetOFF^{hep}$ WAT, which was in contrast reduced in $URI(+/\Delta)^{hep}$ mice on HFD. Therefore, hepatic URI expression might indirectly affect WAT immune status. Moreover, hepatic URI expression partially decreased IRS1 level and increased activation of the lipolytic hormone-sensitive lipase (HLS), which hydrolates TGs stored in WAT into FFA. This phenotype was reversed in HFD-treated $URI(+/\Delta)^{hep}$ mice, strongly supporting the idea that hepatic URI also contributes to WAT IR and lipolysis potentially triggering NASH. Sustained hepatic URI expression also induced pancreatic inflammation and pathological features mimicking human IR and type 2 diabetes. Thus, the authors identified a novel feedforward loop between hepatic URI expression and low-grade systemic inflammation affecting WAT and pancreas, ultimately leading to steatohepatitis.

How dyslipidemia fosters genomic alterations remained unknown. Tummala and colleagues demonstrated that hURI expression induced early genotoxic stress without inflammation (Tummala et al., 2014), suggesting that hepatic hURI induces early genomic alterations. The link between URI expression, DNA damage, and liver inflammation (e.g., macrophage, T cell influx, Kupffer cell activation) was shown using a nicotinamide riboside (NR) diet, which blocks DNA damage by reducing genotoxic stress, inflammation, and steatohepatitis.

Eight-week-old $hURI\text{-}tetOFF^{hep}$ mice displayed elevated IL17A over time, suggesting that IL17A supports neutrophil recruitment.

A role of IL17A in NAFLD has been recently proposed, but its role in NASH, HCC development, and cellular source

and immune cell subtypes was unknown (Harley et al., 2014). Strikingly, Gomes and colleagues also describe IL17A upregulation in CD-HFD- and MCD-fed mice, underlining that upregulation not only of URI but also IL17A is a generic feature of steatohepatitis. Increased IL17A and one of its target genes, lipocalin 2, was also found in hURI-tetOFF^{hep} WAT, whereas HFD-fed URI(+/Δ)^{hep} mice downregulated IL17A. These data suggest a URI-dependent, hepatocyte-derived, cytokine crosstalk between liver and WAT driving NASH.

The authors further linked the URI-dependent systemic low-grade inflammation to Th17 cells using digoxin, a RORγt inhibitor, which suppressed the increase of circulating Th17 cells in hURI-tetOFF^{hep} mice (Figure 1). Digoxin treatment was accompanied by reduced WAT lipolysis, increased glucose tolerance and insulin sensitivity, and reduced IL17A in WAT. Digoxin reduced liver inflammation and injury, diminished early tumorigenesis, and prevented HCC in hURI-tetOFF^{hep} livers. This anti-steatohepatitic, anti-tumorigenic effect of digoxin was corroborated in another fatty-liver-induced carcinogenesis model (Park et al., 2010).

The authors also showed that rIL17A injection in chow-fed C57BL/6 mice mimicked WAT IR and NASH. URI expression was also increased upon rIL17A treatment, indicating a positive feedforward loop. The final proof of concept was accomplished by blocking IL17A in hURI-tetOFF^{hep} mice. IL17A blockade reduced steatohepatitis, fibrosis, and WAT lipolysis, restored WAT insulin signaling, and prevented HCC formation. Several genetic experiments identified myeloid cell populations as one of the main IL17A-receiving cells driving pathology. It will be of interest in the future to determine which exact myeloid cell types located in which organs are key.

Finally, the clinical relevance of their findings, in particular the correlation of URI with IL17A expression, was tested in samples of fatty-liver patients. IL17A was expressed mainly by CD4$^+$ cells, and the number of IL17A$^+$ cells correlated with the patients' steatotic state. Moreover, the authors also showed a positive correlation between URI expression and increased lipid deposition in HCV-infected livers, suggesting a generic role of IL17A in steatohepatitis development, independent of the underlying etiology. Finally, IL17A and IL17RA expression were found in HCC samples, IL17A mainly in the peritumoral tissue, suggesting that IL17A-triggered paracrine signaling might contribute to HCC progression. Indeed, these data strongly suggest that the URI/IL17A axis might influence HCC development in hepatitis virus-infected patients that suffer from NASH.

Together, these results convincingly show that IL17A is one of the master regulators influencing liver, fat tissue and pancreatic inflammation, as well as NASH-driven liver cancer. With efficient anti-IL17A drugs now available, it is tempting to speculate that translation of these data into the clinics is indeed readily feasible in the frame of single or even combinatorial treatments of NASH patients at high risk to develop HCC.

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