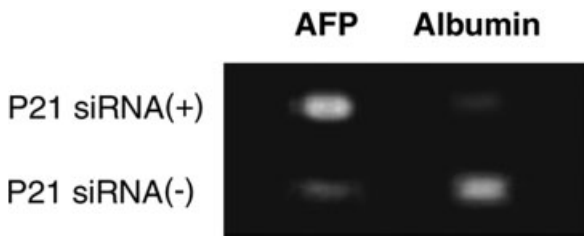

Fig. 1. Expression of albumin.

hepatocyte-like cells. However, we then used human iPSCs while maintaining higher expressions of p21 than p53 in order to avoid tumorigenicity of the human iPSCs and to increase the value of the cells as research tools.[3]

Second, we compared the expression of alfa-fetoprotein (AFP) and albumin between the p21 knockdown group (p21 small interfering RNA [siRNA] (+)) and the control group (p21 siRNA (−)) by reverse transcription polymerase chain reaction (Fig. 1). As a result, the expression of AFP but not albumin was found in the former in 21 days (Fig. 1). Therefore, the human iPSCs could transform to human hepatoma-like cells again during the differentiation induction process to normal hepatocyte-like cells through the knockdown of p21. However, the expression of albumin, but not AFP, was found in the latter in 21 days, indicating that the human iPSCs could also differentiate to normal human hepatocyte-like cells through the expression of albumin in 21 days without knockdown of p21 (Fig. 1).

Third, although aldo-keto reductase family 1 B10 (AKR1B10) is overexpressed in human hepatocellular carcinoma,[4] a review suggests that AKR1B10 inhibits the cellular differentiation produced by retinoic acid.[5] Therefore, we hypothesized that an AKR1B10 inhibitor could be used to enhance the differentiation effects of retinoic acid.

Based on our hypothesis, we tried to investigate the efficacies of acyclic retinoid (10 μM) plus tolestat as an AKR1B10 inhibitor (10 μM) therapy for the human hepatoma-like cells. As a result of this combination therapy, the expression of albumin but not AFP was found in 7 days. Furthermore, we tried to investigate the hepatotoxicities for the combination therapy by using the normal human hepatocyte-like cells. As a result, we found that the activities of glutamic oxaloacetic transaminase (GOT) and lactate dehydrogenase (LDH) in the culture medium of the normal human hepatocyte-like cells increased markedly in the case of acyclic retinoid (30 μM) plus tolestat (30 μM) compared with the case of acyclic retinoid (10 μM) plus tolestat (10 μM), although the efficacies for the combination therapy was not different.

Therefore, acyclic retinoid (10 μM) plus tolestat (10 μM) would be appropriate regimens for human hepatoma-like cells. However, by using the patient-specific hepatocyte-like cells differentiated from human iPSCs of the patients with hepatocellular carcinoma, the efficacies and toxicities of the abovementioned combination therapy for the individual patients with hepatocellular carcinoma will be evaluated more specifically in the near future.

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Hisashi Moriguchi[1,2,3]
Raymond T. Chung[2]
Chifumi Sato[3]
[1]*Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan*
[2]*Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA*
[3]*Department of Analytical Health Science, Graduate School of Health Sciences, Tokyo Medical and Dental University, Tokyo, Japan*

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Lifestyle Intervention and Fatty Liver Disease: The Importance of Both Disrupting Inflammation and Reducing Visceral Fat

To the Editor:

We enthusiastically saw the consistent interest given by Hepatology to the importance of lifestyle interventions in the treatment of both nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Johnson et al.[1] have shown that a 4-week aerobic exercise training per se results in a significant reduction in both hepatic lipids and visceral adipose tissue (VAT). Beside this, Promrat et al.[2] have demonstrated that a 48-week program based on both physical activity and diet-induced weight loss is able to also improve liver histology of patients with NASH. Indeed, these two trials complement each other in clarifying the role of behavioral treatment in the management of chronic fatty liver disease. Along with this, the importance of combined lifestyle therapy (diet plus physical activity) is strongly supported.

The exact mechanisms by which VAT exerts its damaging metabolic consequences remain controversial, but a number of mechanisms have been proposed. It seems likely that both the inflammatory nature of adipose tissue and the amount of abdominal fat accumulation are critical factors in tissue damage. This is what we

have previously observed for cardiac dysfunction and morpho-functional abnormalities.[3,4] Thus, both these targets should be addressed in the treatment. Indeed, NASH develops, and potentially progresses to cirrhosis, on a chronic inflammatory background.[5,6] However, liver disease seems to be associated with systemic degenerative disease and metabolic derangements independently of VAT accumulation.[7]

Adipose tissue is a dynamic organ resulting from the balance of new fat deposition and reabsorption. Several factors are involved in this turnover, such as diet, physical activity, but also inflammation, which is considered per se a major determinant of insulin resistance.[8,9] The portal/fatty acid flux theory suggests that visceral fat, via its unique location and enhanced lipolytic activity, releases toxic free fatty acids, which are delivered in high concentrations directly to the liver. This leads to the accumulation and storage of hepatic fat and the development of hepatic insulin resistance.[9] Nonetheless, a study by van der Poorten et al. has recently shown that visceral fat remained an independent predictor of liver inflammation and fibrosis even when measures of insulin resistance, adipokines, and increasing age are considered.[10]

A 4-week aerobic program can result in a significant reduction of VAT, thus positively affecting the levels of circulating free fatty acids and hepatic lipid accumulation, but appears to be too short a time frame to reduce insulin resistance. Unfortunately, the disruption of inflammatory biomarkers has been not addressed by Johnson et al.[1] This is what Promrat et al. were able to demonstrate,[2] providing evidence that patients undergoing consistent abdominal adipose tissue loss have improved lobular inflammation and also reduced insulin resistance.

Altogether, these results support that both the disruption of inflammation and the reduction of VAT should be targets of therapeutic strategies to reduce local tissue damage. This has been supported for cardiac dysfunction[11,12] and there is some rationale also for treatment of both NAFLD and NASH. However, it must be recognized that it is frequently difficult to keep the patient focused on maintaining changes in lifestyle habits.

Alexis Elias Malavazos, M.D.[1]
Giulia Gobbo, M.D.[2]
Roberta Francesca Zelaschi, M.D.[1]
Emanuele Cereda, M.D., Ph.D.[3]
[1]*Endocrinology Unit, Department of Medical and Surgical Sciences, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Donato, Università degli Studi di Milano, San Donato Milanese, Italy*
[2]*Department of Internal Medicine, Department of Medical and Surgical Sciences, IRCCS Policlinico San Donato, Università degli Studi di Milano, San Donato Milanese, Italy*
[3]*International Center for the Assessment of Nutritional Status (ICANS), Dipartimento di Scienze e Tecnologie Alimentari e Microbiologiche (DISTAM), Università degli Studi di Milano, Milano, Italy*

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Functions and Therapeutic Value of Focal Adhesion Kinase Signaling During Hepatocellular Carcinoma Development and Progression

To the Editor:

We appreciate the article by Wu et al. in a recent issue of Hepatology.[1] In this study, the authors demonstrated that the overexpression of epidermal growth factor–like domain 7 (Egfl7) was closely associated with poor prognosis in hepatocellular carcinomas (HCCs). In addition, they investigated the role of Egfl7 in the development and progression of HCC by silencing its expression via transfecting a specific small interfering RNA in HCC cell lines. Silencing of Egfl7 expression caused no changes in cell growth, even if it resulted in a relevant inhibition of cell migration, which appeared mediated by the phosphorylation of focal adhesion kinase