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A 5:2 intermittent fasting regimen ameliorates NASH and fibrosis and blunts HCC development via hepatic PPARα and PCK1

Suchira Gallage,[1,2,13,*] Adnan Ali,[1,13] Jose Efren Barragan Avila,[1] Nogayhan Seymen,[3] Pierluigi Ramadori,[1,2] Vera Joerke,[4] Laimdota Zizmare,[4,9] David Aicher,[2] Indresh K. Gopalsamy,[2] Winnie Fong,[2] Jan Kosla,[1] Enrico Focaccia,[1] Xin Li,[1] Suhail Yousuf,[5] Tjeerd Sijmonsma,[1] Mohammad Rahbari,[1,6] Katharina S. Kommoss,[1,7] Adrian Billeter,[5] Sandra Prokosch,[1] Ulrike Rothermel,[1] Florian Mueller,[1] Jenny Hetzer,[1] Danijela Heide,[1] Benjamin Schinkel,[2] Tim Machauer,[1] Bernd Pichler,[4,9,12] Nisar P. Malek,[2,8,9] Thomas Longerich,[10] Susanne Roth,[5] Adam J. Rose,[11] Johannes Schwenck,[4,9,12] Christoph Trautwein,[2,4,9] Mohammad M. Karimi,[3] and Mathias Heikenwalder[1,2,9,14,*]

[1]German Cancer Research Center (DKFZ), Division of Chronic Inflammation and Cancer, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

[2]University Tuebingen, Faculty of Medicine, Institute for Interdisciplinary Research on Cancer Metabolism and Chronic Inflammation, M3-Research Center for Malignome, Metabolome and Microbiome, Otfried-Müller-Straße 37, 72076 Tübingen

[3]Comprehensive Cancer Centre, School of Cancer & Pharmaceutical Sciences, Faculty of Life Sciences & Medicine, King's College London, Denmark Hill, London, UK

[4]Werner Siemens Imaging Center, Department of Preclinical Imaging and Radiopharmacy, Eberhard Karls University Tübingen, Röntgenweg 13, 72076 Tübingen, Germany

[5]Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany

[6]Department of Surgery, University Hospital Mannheim, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[7]Department of Dermatology, University Hospital Heidelberg, Heidelberg, Germany

[8]Department Internal Medicine I, University Hospital Tübingen, Tübingen, Germany

[9]Cluster of Excellence iFIT (EXC 2180) "Image-Guided and Functionally Instructed Tumor Therapies," Eberhard-Karls University of Tübingen, Tübingen, Germany

[10]Institute of Pathology, Heidelberg University Hospital, Universitätsklinikum Heidelberg, Pathologisches Institut, Im Neuenheimer Feld 224, 69120 Heidelberg, Germany

[11]Nutrient Metabolism and Signalling Laboratory, Department of Biochemistry and Molecular Biology, School of Biomedical Sciences, and Metabolism, Diabetes and Obesity Program, Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia

[12]Department of Nuclear Medicine and Clinical Molecular Imaging, Eberhard-Karls University of Tübingen, Tübingen, Germany

[13]These authors contributed equally

[14]Lead contact

*Correspondence: s.gallage@dkfz-heidelberg.de (S.G.), m.heikenwaelder@dkfz-heidelberg.de (M.H.)

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SUMMARY

The role and molecular mechanisms of intermittent fasting (IF) in non-alcoholic steatohepatitis (NASH) and its transition to hepatocellular carcinoma (HCC) are unknown. Here, we identified that an IF 5:2 regimen prevents NASH development as well as ameliorates established NASH and fibrosis without affecting total calorie intake. Furthermore, the IF 5:2 regimen blunted NASH-HCC transition when applied therapeutically. The timing, length, and number of fasting cycles as well as the type of NASH diet were critical parameters determining the benefits of fasting. Combined proteome, transcriptome, and metabolome analyses identified that peroxisome-proliferator-activated receptor alpha (PPARα) and glucocorticoid-signaling-induced PCK1 act co-operatively as hepatic executors of the fasting response. In line with this, PPARα targets and PCK1 were reduced in human NASH. Notably, only fasting initiated during the active phase of mice robustly induced glucocorticoid signaling and free-fatty-acid-induced PPARα signaling. However, hepatocyte-specific glucocorticoid receptor deletion only partially abrogated the hepatic fasting response. In contrast, the combined knockdown of *Ppara* and *Pck1 in vivo* abolished the beneficial outcomes of fasting against inflammation and fibrosis. Moreover, overexpression of *Pck1* alone or together with *Ppara in vivo* lowered hepatic triglycerides and steatosis. Our data support the notion that the IF 5:2 regimen is a promising intervention against NASH and subsequent liver cancer.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide and the incidence is expected to rise even further in the coming decades due to the obesity epidemic.[1] NAFLD is considered to be the hepatic manifestation of metabolic syndrome and can progress into more severe forms, such as non-alcoholic steatohepatitis (NASH) and