

# Mechanisms of fibrogenesis in nonalcoholic steatohepatitis and novel therapeutic targets



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The treatment of nonalcoholic steatohepatitis (NASH) is currently based on the reduction of body weight and increase in physical activity, and no pharmacologic therapies are currently approved. Emerging data on the pathophysiology of this condition indicate that hepatic lipotoxicity is an essential component of the chain of events that lead to NASH, triggering hepatic inflammation and activation of myofibroblasts, leading to fibrosis and cirrhosis. In addition, the biology of the liver is markedly influenced by signals provided by other tissues, particularly the white adipose tissue, through enhanced flow of free fatty acids, and adipokines. Increasing attention is also directed to the role of the microbiome and to bacteria-derived products that reach the liver through the portal circulation. Other 'extrahepatic hits' may be related to dietary factors and gastrointestinal hormones. Within the liver, lipotoxicity and other factors determine activation of Kupffer cells and appearance of inflammation, involving leukocytes recruited from the bloodstream. Development and maintenance of inflammation and fibrogenesis involves chemokines, the cannabinoid system, assembly of the inflammasome and activation of pattern-recognition receptors.

I will review the major mechanisms leading to appearance and progression of NASH, focusing on adipose tissue-derived signals and local inflammatory mechanisms, in an effort to identify the most promising molecular targets for the treatment of this condition.

## Curriculum Vitae

Dr. Marra graduated cum laude in 1986 at the University of Florence, School of Medicine. He received his Ph.D. Degree in 1992, with studies on the pathophysiology of cirrhosis. From 1992 to 1994 he has been Post-doctoral Fellow in the Department of Medicine, University of Texas Health Science Center at San Antonio USA. In 1995 Dr. Marra has been appointed Assistant Professor of Medicine at the University of Florence, School of Medicine, where he leads an independent research group. Since 2004 he is Associate Professor of Medicine. In addition to his research activity, Dr. Marra is involved in clinical work and teaching in the Department of Medicine.

From 2002 to 2005 Dr. Marra has been a member of the Steering Committee of the Italian Association for the Study of the Liver (AISF). From 2007 to 2010 he has been a member of the Governing Board of the European Association for the Study of the Liver (EASL). He has published more than 100 papers on peer-reviewed journals, and is a member of the Editorial Board of major international journals, including Gastroenterology, Gut, Clinical Science, American Journal of Physiology - GI & Liver. Dr. Marra regularly serves as a reviewer for the most important gastroenterology journals and for funding agencies. He is currently Associate Editor of Journal of Hepatology and Liver International.

Dr. Marra's group has provided a relevant scientific contribution to several fields of Hepatology, including the cellular and molecular mechanisms of hepatic inflammation and fibrogenesis, pathophysiology of nonalcoholic steatohepatitis, and non-invasive evaluation of liver fibrosis.