

Under-studied Genes That are Likely Associated with Liver Aging

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Abstract

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1. Introduction

The liver is a central hub of metabolism, detoxification and immune surveillance, and its functional decline is a hallmark of organismal ageing. Epidemiological surveys consistently show that the burden of liver-related malignancies rises with population ageing; liver cancer accounted for more than half a million new cases worldwide in the year 2000 and its incidence continues to increase as life expectancy grows [1–3]. Parallel to this trend, non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH), are projected to affect over one-third of adults by 2030, with the median age of the affected population shifting upward, thereby amplifying the risk of cirrhosis and hepatocellular carcinoma in older individuals [4].

Ageing-associated chronic low-grade inflammation (inflammaging) creates a permissive environment for hepatic injury and tumorigenesis [5]. In the liver, senescent hepatocytes and hepatic stellate cells adopt a senescence-associated secretory phenotype (SASP) that fuels fibrosis and malignant transformation, a process that can be exacerbated by obesity-derived gut microbial metabolites such as deoxycholic acid [6]. Cellular senescence is also a key effector of tumour suppression; re-activation of p53 in murine liver carcinomas triggers a robust senescence programme that engages innate immunity to clear tumour cells [7].

Metabolic dysregulation contributes further to hepatic ageing. The NAD⁺-dependent deacetylase SIRT1 modulates hepatic gluconeogenesis and mitochondrial biogenesis through deacetylation of PGC-1, linking

nutrient signals to age-related metabolic decline [8]. Age-related depletion of glutathione impairs antioxidant capacity, rendering the liver more vulnerable to oxidative stress and age-associated diseases [9]. Moreover, tissue-resident macrophages (Kupffer cells) derived from embryonic progenitors persist throughout life, but their functional capacity wanes with age, influencing liver immunity and repair [10].

The regenerative potential of the aged liver is also compromised. Hepatic progenitor cell proliferation declines due to epigenetic repression of Notch signalling, yet exposure to a youthful systemic milieu can rejuvenate these cells, restoring proliferative capacity [11]. Pharmacological mimetics of caloric restriction, such as resveratrol, improve metabolic health and extend survival in aged mice, highlighting the therapeutic promise of targeting ageing pathways in the liver [12].

Collectively, these studies delineate a multifactorial landscape in which genomic instability, metabolic rewiring, chronic inflammation, and stem-cell exhaustion converge to drive liver ageing and its associated pathologies. Understanding these interconnected mechanisms is essential for developing interventions that preserve hepatic function in the ageing population.

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