



Hepatocyte Fate Transitions in Progressive Liver Disorders

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DESCRIPTION

The traditional idea of cellular senescence has long been associated with an irreversible halt in cell division that occurs as a response to stress, DNA damage, or excessive replication. In the liver, however, this view is undergoing a gradual transformation as researchers recognize that hepatocytes experience a more complex set of fate changes during chronic and acute liver conditions. Rather than existing solely as inactive bystanders, senescent hepatocytes appear to participate in broader biological responses that influence inflammation, regeneration, fibrosis and even malignant transformation. Redefining senescence through the study of hepatocyte fate changes allows a deeper appreciation of how liver diseases progress and how they may be better managed in the future.

The liver is composed mainly of hepatocytes, which serve essential functions in metabolism, detoxification, bile production and protein synthesis. These cells possess an extraordinary capacity for regeneration compared to many other tissues. Following injury, hepatocytes can re-enter the cell cycle and restore lost tissue mass, maintaining structural and functional stability. When damage is repeated or sustained for extended periods, as in chronic viral hepatitis, fatty liver disease, alcohol-related injury, or autoimmune disorders, hepatocytes undergo cellular adaptations. Among these adaptations is senescence, which once was viewed as a protective mechanism that stops the propagation of damaged cells. Recent studies indicate that senescent hepatocytes are not simply dormant. Instead, they secrete a combination of inflammatory mediators, growth factors and enzymes that influence neighboring cells and modify the liver microenvironment.

In aging individuals, the burden of senescent hepatocytes naturally increases. This accumulation explains, in part, the increased vulnerability of older livers to metabolic disorders and fibrosis. In people with underlying liver disease, the process accelerates. Non-alcoholic fatty liver disease presents a clear example, where lipid overload and oxidative stress alter hepatocyte structure and DNA stability. These changes push cells toward a senescent phenotype. The altered metabolic status

of these cells also disrupts insulin signaling and lipid processing, contributing to more widespread metabolic imbalance.

A growing area of interest in hepatology is the reversibility of the senescent state. Earlier thinking suggested that, once a cell entered senescence, it could not return to active division. Recent findings challenge this assumption in hepatocytes, especially in animal models. Under specific conditions, some hepatocytes showing signs of senescence regain limited capacity to divide and contribute to regeneration. This discovery creates new questions about the stability of cell fate and the molecular switches that control it. Epigenetic modifications, mitochondrial function and cellular signaling networks seem to play roles in determining whether a hepatocyte remains in a senescent state or reenters a regenerative pathway.

The immune system plays an influential role in shaping the outcome of senescent hepatocytes. When immune surveillance is effective, macrophages and natural killer cells recognize and eliminate dysfunctional cells. This process reduces the overall number of senescent cells and promotes tissue renewal. In chronic conditions, however, immune exhaustion occurs. This leads to impaired clearance and an accumulation of senescent hepatocytes. The persistence of such cells alters the structural and biochemical environment of the liver and contributes to progressive functional decline.

Therapeutic interest now extends toward agents that selectively remove senescent cells, often called senolytics. Although research in this area is still developing, early studies suggest that clearing senescent hepatocytes can improve liver function and reduce fibrosis in experimental models. Another approach involves senomorphics, which do not remove cells but reduce their harmful secretory profile. These strategies offer an alternative pathway to managing liver disease beyond suppressing inflammation or inhibiting fibrosis alone. By targeting the cellular aging process itself, clinicians may one day slow or even reverse aspects of chronic liver damage.

In conclusion, redefining senescence through hepatocyte fate changes expands the understanding of liver disease well beyond the classical view of irreversible growth arrest. Hepatocytes in a

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senescent state remain active contributors to the liver environment, affecting inflammation, fibrosis, regeneration and even cancer development. Their presence is influenced by aging, metabolic stress, infection, toxins, immune efficiency and genetic integrity. By studying these processes more deeply, medicine moves closer to strategies that modify cell fate, improve

liver repair, reduce chronic damage and enhance long-term function. This evolving perspective represents a significant step in understanding how the liver adapts to long-term stress and how the processes of cellular aging can be better managed in the context of disease.