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Sex-related variations in liver homeostasis and disease: From zonation dynamics to clinical implications

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Abstract

The liver exhibits pronounced sexual dimorphism, characterised by sex-specific differences in structure, metabolic function, and susceptibility to disease. Although traditionally considered homogeneous, the liver exhibits significant zonal heterogeneity, with periportal and pericentral regions differing considerably in terms of oxygen availability, metabolic activity and cellular composition. In recent years, new technologies, such as single-cell RNA sequencing and spatial proteomics, have revealed numerous sex-specific differences in gene and protein expression that align with the spatial heterogeneity of liver functions. These spatial and functional dynamics are largely influenced by sex hormones, including oestrogens, androgens, and growth hormone, and their downstream endocrine signalling pathways. Consequently, men and women not only differ in their susceptibility to various liver diseases, but also in the rate and pattern of disease progression, including fibrogenesis. For instance, men are more prone to developing MASLD (metabolic dysfunction-associated steatotic liver disease) and HCC (hepatocellular carcinoma), whereas women have a higher prevalence of autoimmune liver diseases and are at increased risk of accelerated fibrosis progression after menopause. Digital twin models and innovative computer-assisted approaches continue to advance our understanding of liver dimorphism, offering the prospect of personalised strategies for diagnosis and treatment.