The Ageing Liver

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The liver carries out numerous separate metabolic and detoxification functions which are essential for maintaining human health. Supporting these functions are the dense networks of blood vessels called sinusoids and the highly specialized liver sinusoidal endothelial cells (LSEC) that line these vessels.

The LSEC occupies a strategic position in the liver, separating blood in the sinusoid from the surrounding liver cells. It has long been recognized that LSECs have a role facilitating, and perhaps regulating, the transfer of substrates between the blood and the liver parenchyma, forming a blood-liver cell barrier. LSECs have a unique morphology compared to other endothelial cells, which underpin their physiological role in substrate transfer. The cytoplasmic extensions of LSECs are very thin and perforated with transcellular holes called fenestrations that are true discontinuities in the endothelium. The fenestrations permit the passage of a wide range of substrates (plasma and substrates within plasma, plasma proteins including medications, toxins, albumin, insulin, smaller lipoproteins and colloidal particles) into the underlying liver cells for further processing. The fenestrated LSEC acts as a filter and hence was termed ‘the liver sieve’.

There are numerous reports of diseases and pathological processes that influence fenestrations, including: liver disease, exposure to liver toxins and most significantly, ageing.

Age-related pseudocapillarization is now well documented, the most recognised features being loss of endothelial fenestrations, endothelial thickening and increased deposition of extracellular matrix. These changes substantially impact upon liver function, in particular leading to a reduction in the transfer of lipids and pharmaceutical agents, increasing the burden of disease for older people.

We have recently discovered that the arrangements of lipids and proteins in the cell membrane are integral in fenestration formation and maintenance. We have called this the “Sieve-Raft hypothesis” and believe it is a major step toward a greater understanding of fenestrations and importantly, how we can prevent their loss in ageing and potentially lessen the disease burden of older people.