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The role of albumin receptors in regulation of albumin homeostasis: implications for drug delivery

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Abstract

Albumin is the most abundant protein in blood and acts as a molecular taxi for a plethora of small insoluble substances such as nutrients, hormones, metals and toxins. In addition, it binds a range of medical drugs. It has an unusually long serum half-life of almost 3 weeks, and although the structure and function of albumin has been studied for decades, a biological explanation for the long half-life has been lacking. Now, recent research has unravelled that albumin-binding cellular receptors play key roles in homeostatic regulation of albumin. Here, we review our current understanding of albumin homeostasis with a particular focus on the impact of the cellular receptors, namely the neonatal Fc receptor (FcRn) and the cubilin-megalin complex, and we discuss their importance on uses of albumin in drug delivery.

Introduction

Albumin is exclusively synthesised by specialized liver hepatocytes that direct secretion into the circulation. Here, albumin constitutes an incredible 60% of the total protein pool. In humans, this gives rise to an average plasma concentration of 40 mg/ml, (600 μM), and a total amount of 360 g in a 70 kg person. The large investment in synthesis is interesting from an evolutionary perspective, as it suggest that the energy used is of great importance to maintain health.

In the blood, albumin performs a number of important functions including the maintenance of oncotic pressure, regulation of the pH as well as transport and distribution of a plethora of insoluble and hydrophobic endogenous and exogenous ligands, such as metals, fatty acids (FAs), hormones, amino acids, waste products, toxins and medical drugs. In addition, albumin is an antioxidant and even possesses enzymatic properties [1–3].

Another unique feature of albumin, is its long serum half-life of nearly three weeks in humans, which it shares with another abundant blood protein, the immunoglobulin G (IgG) [4–6]. Despite these proteins being completely unrelated, both structurally and functionally, it has been demonstrated that they both bind simultaneously to a ubiquitously expressed cellular receptor named the neonatal Fc receptor (FcRn). This receptor is responsible for salvaging both IgG and albumin from degradation via cellular mechanisms that are strictly regulated by pH dependent binding to the receptor [7–10]. The literature also describes several other putative albumin receptors, but they are poorly characterized and their role in albumin homeostasis has not yet been fully addressed. The cubilin-megalin complex is one exception, which, in additional to FcRn, has recently been demonstrated to be of importance in retrieval of albumin from the kidneys. However, how albumin-bound ligands may affect interactions and transport properties of the receptors has not been extensively investigated.