Albumin

A protein with a multitude of functions
Overview

The albumin molecule

Albumin distribution, metabolism and binding

Albumin in fluid homeostasis

Other functions of albumin
The albumin molecule
The albumin molecule

- Single polypeptide chain
  - 585 amino acids
  - 66 kDa molecular weight
- Negatively charged
- Non-glycosylated

Serum albumin. Reproduced with permission from David Goodsell & RCSB Protein Data Bank, 2013.

Albumin distribution, metabolism and binding
Albumin distribution

~350 g total\(^1\)

~40% intravascular\(^2\)

~60% extravascular\(^2\)

Albumin metabolism

- Up to 14 g of albumin is synthesized daily\(^1\)
- Site of synthesis:\(^1\)
  - Liver
- Regulators of synthesis:\(^1,2\)
  - Colloid osmotic pressure (COP)
  - Cortisol and thyroid hormone
- \(~4\%\) of the albumin pool is degraded daily\(^1\)

COP, colloid osmotic pressure
Albumin binding

- Many albumin functions are mediated by ligand binding
- Albumin is endowed with multiple specific binding sites

- Fatty acids
- Bilirubin
- Haem
- ROS
- Calcium
- Copper
- Iron
- Nitric oxide

- Tryptophan
- Glucocorticoids
- Thyroxine
- Vitamins
- Amyloid-β
- Endotoxin
- Drugs
- Contrast agents

Albumin bound to 7 arachidonic acid molecules. Reproduced with permission from David Goodsell & RCSB Protein Data Bank, 2013.

ROS, reactive oxygen species
Therapeutic drugs bound by albumin

**NSAIDs**
- Ibuprofen
- Naproxen
- Indomethacin
- Phenylbutazone
- Salicylates

**Antimicrobials**
- Cephalosporins
- Penicillins
- Sulfonamides
- Tetracyclins
- Vancomycin

**Cardiovascular**
- Digitoxin
- Hydralazine
- Propranolol
- Quinidine
- Verapamil

**Anxiolytics**
- Diazepam
- Midazolam
- Lorazepam
- Phenobarbital

**Antidepressants**
- Amitriptyline
- Chlorpromazine
- Imipramine

**Chemotherapy**
- Cisplatin
- Paclitaxel
- Tamoxifen

**Anaesthetics**
- Propofol
- Halothane
- Thiopentone

**Diuretics**
- Furosemide
- Thiazides
- Carbonic anhydrase inhibitors

**Anti-epileptics**
- Valproate
- Phenytoin

**Other**
- Warfarin
- Clofibrate
- Glipizide

NSAIDs, non-steroidal anti-inflammatory drugs
Albumin in fluid homeostasis
Albumin in fluid homeostasis

- Albumin supplies 80% of total plasma COP
- Albumin retards:
  - Fluid efflux from plasma
  - Oedema formation

**Net filtration pressure (mm Hg)**

- Arteriolar: 15 mm Hg
- Venular: -3 mm Hg

**Arteriolar hydrostatic pressure gradient (mm Hg)**

- 2 mm Hg COP
- 15 mm Hg arteriolar pressure
- 37 mm Hg interstitial COP

**Venular hydrostatic pressure gradient (mm Hg)**

- 2 mm Hg COP
- 3 mm Hg venular pressure
- 20 mm Hg interstitial COP

COP, colloid osmotic pressure
Other functions of albumin
Other functions of albumin

- Albumin is involved in numerous other functions, many due to binding, including:
  - Transport/delivery
  - Detoxification
  - Reservoir (i.e. provides storage) for signalling molecules and nitric oxide
  - Acid–base balance
  - Apoptosis
  - Cell proliferation
  - Oxidation–reduction
  - Immunomodulation

Fatty acid transport/delivery

- Fatty acids (FA) are essential for:
  - Energy metabolism
  - Synthesis of membrane phospholipids and regulatory mediators

- Albumin:
  - Binds and solubilizes FA
  - Is the main protein binding FA in extracellular fluids
  - Plasma albumin delivers FA to vascular endothelium
  - Interstitial albumin transports FA to target tissues

FA, fatty acids
van der Vusse. *Drug Metab Pharmacokinet* 2009; 24: 300–307
Detoxification of bilirubin

- The majority of circulating unconjugated bilirubin is bound to albumin
- Albumin solubilizes bilirubin and neutralizes its toxic effects
- Albumin transports bilirubin to the liver
- In the liver, bilirubin:
  - Dissociates at the sinusoidal surface of hepatocytes
  - Undergoes conjugation and excretion in bile

Serum albumin. Reproduced with permission from David Goodsell & RCSB Protein Data Bank, 2013.
Extracorporeal detoxification

- Accumulation of albumin-bound metabolites occurs in liver failure
- Albumin-bound substances in plasma are decreased by extracorporeal albumin dialysis including:
  - Bilirubin
  - Bile acids
  - Tryptophan
  - Middle- and short-chain FA
  - Aromatic amino acids
  - TNF-α
  - IL-6
  - Copper
  - Diazepam

FA, fatty acids; TNF, tumour necrosis factor; IL, interleukin
Nitric oxide reservoir

Nitric oxide (NO) has diverse actions, including:
- Vasodilation
- Platelet aggregation
- Neutrophil adhesion
- Superoxide production and removal

Plasma NO is mostly covalently bound to albumin
- S-Nitrosylated adduct (SNO-albumin) forms at cysteine 34

SNO-albumin is more stable than low-molecular weight S-Nitrosothiols

NO is released from the SNO-albumin reservoir as needed by:
- Transfer to low-molecular weight thiols
- SNO-albumin binding to albumin cell surface receptor
SNO-albumin in cardiopulmonary bypass

- In the ischaemia/reperfusion model, SNO-albumin increased:
  - Mean arterial pressure
  - Cardiac energetic reserve

SNO-albumin, S-nitrosylated adduct
Acid–base balance

- Stewart model of acid–base balance
- 3 independent variables govern acid–base balance:
  - $pCO_2$
  - Total concentration of weak acids ($A_{TOT}$)
  - Strong ion difference (SID)
- Albumin is the main determinant of $A_{TOT}$

$A_{TOT}$, total concentration of weak acids; SID, strong ion difference
**Apoptosis**

- Albumin prevents apoptosis of proximal renal tubular cells
  - Effective at physiological albumin concentrations
- This activity is independent of both bound lipid and COP

Cell proliferation

- Albumin stimulates proliferation of proximal renal tubular cells
  - Effective at physiological albumin concentrations
- Maintains proximal tubular integrity/function
Oxidation–reduction

- Diverse oxidation–reduction reactions are affected by albumin
- Cysteine 34 of the albumin polypeptide chain
  - Participates reversibly in oxidation–reduction reactions
  - Provides 80% of plasma thiols
  - Major contributor to total plasma antioxidant capacity
- Binding to albumin can influence oxidation–reduction
  - Albumin binds and inactivates pro-oxidant Cu^{2+}
  - Unsaturated FA are protected from oxidation by binding to albumin
  - Albumin-bound bilirubin is endowed with antioxidant activity

Antioxidant activity

- Blockade by albumin of:
  - Cu$^{2+}$-mediated LDL oxidation
  - Free-radical-mediated haemolysis

LDL, low-density lipoprotein
Immunomodulation

• An immune response is central for:
  – Host response to infection
  – Damage repair

• But an overexuberant response can be harmful, for example:
  – SIRS after cardiac surgery
  – Excessive capillary permeability during shock

• Albumin:
  – Is free of the pro-inflammatory effects exhibited by other resuscitation fluids
  – Displays immunomodulatory activity

SIRS, Systemic Inflammatory Response Syndrome
Pro-inflammatory effects of resuscitation fluids

- Whole blood from volunteers diluted 75% in vitro with test fluids
- Crystalloids and artificial colloids showed significant pro-inflammatory effects
- No significant effect of 5% or 25% albumin

Prevention of haem-mediated delay in neutrophil apoptosis

- Haemolysis causes a release of haem
  - Frequent in cardiac surgery
- Haem is known to be pro-inflammatory and probiotic
- Haem mediates a delay in neutrophil apoptosis
  - This effect is blocked by albumin
- Therefore, the replacement of albumin in a bypass circuit may avert the pro-inflammatory and probiotic effects of haemolysis

Bundy et al, Am J Respir Crit Care Med 2010; 181: A2798
Host cell response to Gram-negative bacteria

- Albumin forms a complex with:
  - Lipopolysaccharide (LPS)
  - Soluble CD14 (sCD14)
- This complex acts on toll-like receptor 4
- IL-8 is generated
- Albumin is an essential facilitator of the response to endotoxin

LPS, lipopolysaccharide; sCD14, soluble CD14; IL-8, interleukin-8
Gioannini et al, J Biol Chem 2002; 277: 47818–47825
Conclusions

- Albumin is a central mediator of physiological homeostasis
  - Albumin maintains fluid balance by maintaining COP
- Albumin has numerous other functions, many due to binding, including:
  - Transport/delivery
  - Detoxification
  - Reservoir
  - Acid–base balance
  - Apoptosis
  - Cell proliferation
  - Oxidation–reduction
  - Immunomodulation
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