

A Protective Role of Fetuin-A, In heart failure and diabetes activities

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Received for publication: Jan 11th 2013; Revised: Feb 4th 2013; Accepted: Feb 21st 2013

Abstract: Human fetuin is synonymous with α 2-HS-glycoprotein (genetic symbol AHSG), α 2-HS, A2HS, AHS, HSGA, and fetuin-A. Fetuin-A exists as a single-copy gene in the human and mouse genomes. A closely related gene, fetuin-B, also exists in the human, rat, and mouse genomes. Like fetuin-A, fetuin-B is made predominantly by the liver and to a lesser extent by a number of secretory tissues. Fetuins exist in all vertebrate genomes including fish and reptiles. Fetuins are members of a family of proteins that evolved from the protein cystatin by gene duplication and exchange of gene segments. Fetuins thus belong to the cystatin super family of proteins. Fetuin relatives within this super family are the histidine-rich glycoprotein (HRG) and kininogen (KNG). Fetuins are blood proteins that are made in the liver and secreted into the bloodstream. They belong to a large group of binding proteins mediating the transport and availability of a wide variety of cargo substances in the bloodstream. The best known representative of these carrier proteins is serum albumin, the most abundant protein in the blood plasma of adult animals. Fetuin is more abundant in fetal blood, hence the name "fetuin" (from Latin, fetus). Fetal calf serum contains more fetuin than albumin, while adult serum contains more albumin than fetuin.

Keywords: α 2-HS, A2HS, AHS, Fetuin, Glycoprotein.

Introduction

Fetuin (also designated α -2- ζ -globulin or α -2-HS-glycoprotein) is a secreted plasma protein that is expressed in hepatocytes, monocyte / macrophages and in bone and is down regulated during injury and inflammation. Fetuin preferentially binds to and carries calcium and barium ions in the blood, where it is thought to mediate serum calcium homeostasis and mineralization, and to potentially participate in the transport of bioactive molecules¹. Additionally, fetuin has been shown to function as an acute phase anti-inflammatory mediator that is critical to regulating the innate immune response following tissue injury. During inflammation, circulating fetuin levels substantially decrease as fetuin becomes associated with the membranes of macrophages. This membrane associated form of fetuin acts as an opsonic participant by potentiating the entry of cationic small molecules into the activated macrophage, which in turn facilitates macrophage deactivating mechanisms². Biologically active fetuin is derived from a precursor protein that is cleaved at the amino-terminus to generate two chains held together by a single disulfide bond. There is a protective role of fetuin-a, in heart failure and diabetes activities. Anti-inflammatory role of Fetuin-A, Fetuin-A in Metabolic Syndrome, Role of Fetuin-A in Mineralization Biology, Calciprotein Particles Metabolism and Clearing³.

Fetuin-A Biosynthesis:

Fetuins are highly expressed liver-derived plasma proteins bearing posttranslational modifications proteolytic processing, complex glycosylation, phosphorylation and sulfation⁴. Human fetuin-A/2-HS glycoprotein is processed from a single-chain precursor to the mature circulating two-chain form. Human fetuin-A is susceptible to further proteolytic cleavage in septicemia, and bovine fetuin-A is processed by matrix

metallo proteinases. Figure.2, illustrates secondary modifications and allelic variants identified in human fetuin-A/2-HS glycoprotein. These modifications may regulate protein expression levels, stability, and biological activity. Phosphorylation is indispensable for fetuin-A interaction with the insulin receptor, whereas phosphorylation seems not to be required for mineral interaction. Desialylation will result in immediate hepatic clearing through the asialoglycoprotein receptor⁵.

Binding Properties of Fetuin-A:

The type 3 members of the cystatin super family are glycoproteins produced mainly in the liver, which circulate in plasma at high concentrations. Fetal calf serum contains more fetuin-A than albumin. Apart from the vasculature, fetuins are present throughout the extracellular spaces and the extracellular matrix. Given the high expression levels and the many possible ways of molecular interaction with multiple ligands, it is fair to assume that fetuins primarily exercise carrier and scavenger functions like albumin⁶. This poses an important complication for ex vivo experimentation, because crude fetuin preparations contain impurities. Like pure albumin preparations, pure fetuin preparations are difficult to make. High-abundance plasma protein preparations are notoriously, shown as fig.1. Contaminated with lower-abundance biological molecules that co-purify either because of natural association or because of mere coincidence.

Various growth factors or growth promoting:

Substances associate with crude fetuin preparations and form the basis of the "enigmatic growth promoting properties" of fetuin in cell culture. Whether associations of fetuin-A with certain ligands are physiologically relevant is a matter of controversy and is almost impossible to decide

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unless genetic models are developed to test such interactions *in vivo*⁷. We remind readers to heed the old wisdom of Racker that also became part of the "10 commandments" of Kornberg, "Do not waste clean thinking on dirty enzymes."

Most commercial preparations of fetuin-A on the market today do not go much beyond the quality of "fetuin" from 1944, which is better viewed as a "protein concept" like "globulin" or "albumin" rather than a clean product. We distinguish between fetuin and fetuin-A whenever possible⁸. Also, before the year 2000 when fetuin-B was cloned in silica and the year 2003 when it was finally shown to be expressed as a plasma protein, both fetuin-A and fetuin-B were collectively addressed as "fetuin," and most fetuin sold today is not screened for the presence of fetuin-B. Studies of human 2-HS glycoprotein/fetuin (2-HS glycoprotein) will always signify fetuin-A.

Publications studying "fetuin" protein are probably dealing with fetuin-A as well, but it is impossible to exclude that fetuin-B was also studied because of the physicochemical similitude of both proteins. Fetuin-A binding is prodigious and reaches from small molecules to entire organisms^{9,10}. Plasmodium sporozoites use fetuin-A binding to "hitch-hike" their way into liver cells, suggesting that fetuin-A function is indispensable and despite negative selection pressure has been maintained long enough for this docking mechanism to evolve. Soon after its discovery, Fetuin has been shown to inhibit trypsin, shown as fig: 2

A protective roles of fetuin-A

Anti-inflammatory Role of Fetuin-A:

Fetuin-A, one of the most abundant fetal plasma proteins, was found to be essential for the inhibition of the pro-inflammatory cytokine tumor necrosis factor production by spermine and its synthetic analogues. Accordingly, the strong fetal expression of fetuin and spermine has been associated with the tolerance of the fetus, nature's transplant, by mothers. The strong anti-inflammatory effects of fetuin were verified *in vivo* using several models of inflammation, including lip polysaccharide-induced miscarriage in rats, carrageenan injection, cerebral ischemic injury in rodents, and cecal ligation and puncture in mice¹¹. In all cases fetuin-A was associated with reduced inflammatory response and increased survival, and administering additional fetuin generally improved outcome. Thus fetuin-A generally may be regarded as anti-inflammatory¹². The anti-inflammatory property of serum α 2-HS glycoprotein/human fetuin-A was further supported by the demonstration that fetuin-A is a potent and specific crystal-bound inhibitor of neutrophil stimulation by hydroxyapatite crystals. Calcium phosphate crystals induce pro inflammatory cytokine secretion through the NLRP3 inflammation in monocytes/macrophages, cell death in human

vascular smooth muscle cells, and cell activation in chondrocytes. Antiapoptotic activity of fetuin-A has been observed in smooth muscle cells and dampening of the cell-specific responses would generally be expected to alleviate the detrimental consequences of local inflammation, cell death, and cartilage degradation. The proven protective function of fetuin-A in many animal models of inflammation, the inhibition of pro inflammatory compounds, and the inhibition of crystal-induced neutrophil activation collectively suggest that fetuin-A may generally protect during pathological mineralization as well¹³.

Calciprotein Particles Metabolism and Clearing:

Illustrates the putative metabolism of calciprotein particles, soluble protein-mineral complexes, which are now regarded as a physiological byproduct of mineral metabolism¹⁴. The scheme is partly hypothetical and requires experimental verification. Soluble protein-mineral complexes including fetuin-A have been detected in serum from etidronate overdosed rats, in adenine treated rats, in peritoneal dialysis patients with sclerosing calcifying peritonitis, and in dialysis patients. The scheme is modeled after lipoprotein particle metabolism, a well-known transport system for otherwise insoluble lipids like cholesterol esters, shown as fig: 3 & 4.

The basic tenet of calciprotein particles metabolism holds that fetuin-A stabilizes mineral complexes and at the same time mediates their transport and clearing. Fetuin-A should be regarded as an opsonizing serum protein with a high affinity for mineral complexes and debris. The opsonizing properties of fetuin-A have been determined several decades ago. Fetuin-A affects micro particle phagocytosis by dendritic cells, phagocytosis of apoptotic cells by macrophages, and opsonizes phospholipids particles¹⁵. Fetuin-A is, however, not generally sticky like the "big 12" plasma proteins, which adhere to most materials in blood contact, and fetuin-A was also not listed among specific proteins interacting with sepharose beads in a study that used quantitative mass spectrometry to determine bead proteomes. Therefore, binding may be restricted to a narrow range of cationic, lipidic, or mineral ligands and a few more interacting TGF- β -related cytokines mentioned earlier in this text^{16, 17, 18}. Given the high abundance of fetuin-A in plasma, any clearing mechanism would have to rely on conformational or structural changes in fetuin-A or on multivalent binding that turns low-affinity binding into high-avidity binding. Uptake of fetuin-A by cultured human vascular smooth muscle cells has been demonstrated, but the exact form of fetuin-A was not determined¹⁹. Clustering of fetuin-A molecules on the surface of secondary calciprotein particles as demonstrated¹¹ ideally fulfills the ligand clustering required to increase binding strength. Our preliminary results of fetuin-A

monomer and fetuin-A containing calciprotein particle clearing in vivo show that calciprotein particles are cleared vastly more efficiently than fetuin-A monomer. Nevertheless, specific receptors for calciprotein particle clearing discriminating against fetuin-A monomer remain to be determined.

Protective roles of fetuin-An in atherosclerosis:

If atherosclerosis leads to symptoms, some symptoms such as angina pectoris can be treated²⁰. Non-pharmaceutical means are usually fetuin-An in atherosclerosis role play the first method of treatment, If these methods do not work, medicines are usually the next step in treating cardiovascular diseases, and, with improvements, have increasingly become the most effective method over the long term, shown as fig: 5.

Primary and secondary prevention:

Atherosclerosis demonstrates by the accumulation of lipids, connective tissue and inflammatory cells in the intima-media layer of the arterial wall. There are various factors that support the development of atherosclerosis: insulin resistance, hyperuricaemia, age, sex, lipid disturbances. Mitral and aortic annuli calcification is linked to atherosclerosis. A uraemia associated factor like inflammation or oxidative stress may contribute to accelerated atherogenesis and hence increases the risk for cardiovascular diseases. Malnutrition and inflammation finally accelerates atherosclerosis²². Patients with CKD are at increased risk of atherosclerosis. Hyperglycaemia produces various changes in the vascular tissue at the cellular level that accelerates the atherosclerosis. There is a direct correlation among carotid arterial stiffness and the serum fetuin-A level. It is a calcium regulatory glycoprotein and inhibits vascular calcification, which is related to the inflammation. Fetuin-A is an inhibitor of ectopic calcification. Fetuin-A is a marker of the inflammatory nutritional state and acts as a protective agent because it solubilizes the calcium phosphate salt.

Protective roles of fetuin-in diabetes:

Method of measurement:

Fetuin-A is associated with type-2 diabetes because in humans a higher concentration of it causes insulin resistance. Various circulating proteins like fetuin-A and adiponectin regulate insulin sensitivity. When fetuin-A is administered in rodents it inhibits the tyrosine phosphorylation of the insulin receptor in skeletal muscle and liver of rats²³. Insulin resistance and metabolic syndrome is the indicator of a high level of fetuin-A in the blood circulation and this condition increases the chances of cardiovascular disease²⁴. Susceptibility to type-2 diabetes is strongly related to the position of the gene encoding for fetuin-A. This gene is present on

the 3q27 chromosome and this location is responsible for metabolic syndrome and type-2 diabetes. Fetuin-A has radiogenic properties and the gene for fetuin-A and human adiponectin is present on chromosome 3q27, almost next to one another. Adiponectin is mainly secreted by adipose tissue and determines cardiovascular disease and insulin sensitivity. Previously, this location mapped as a metabolic syndrome and type-2 diabetes susceptibility locus. A person without a history of diabetes in the family may have the risk of diabetes due to adiponectin polymorphism, because the gene for adiponectin is located on chromosome 3q27, which is the susceptibility locus for type-2 diabetes and metabolic syndrome. Polymorphism of adiponectin may increase the risk of obesity and insulin resistance secondarily.

Treatment:

Treatment of some forms of hypoglycemia, such as in diabetes, involves immediately raising the blood sugar to normal through the ingestion of carbohydrates, determining the cause, and taking measures to hopefully prevent future episodes. However, this treatment is not optimal in other forms such as reactive hypoglycemia, where rapid carbohydrate ingestion may lead to a further hypoglycemic episode. Blood glucose can be raised to normal within minutes by taking (or receiving) 10-20 grams of carbohydrate²⁵. It can be taken as food or drink if the person is conscious and able to swallow. This amount of carbohydrate is contained in about 3-4 ounces (100-120 ml) of orange, apple, or grape juice although fruit juices contain a higher proportion of fructose which is more slowly metabolized than pure dextrose, alternatively, about 4-5 ounces (120-150 ml) of regular (non-diet) soda may also work, as will about one slice of bread, about 4 crackers, or about 1 serving of most starchy foods. Fetuin- is quickly digested to glucose (unless the person is taking oral hypoglycemic agents), but adding fat or protein retards digestion. Symptoms should begin to improve within 5 minutes, though full recovery may take 10–20 minutes²⁶. Overfeeding does not speed recovery and if the person has diabetes will simply produce hyperglycemia afterwards. A mnemonic used by the American Diabetes Association and others is the "rule of 15" - consuming 15 grams of carbohydrate followed by a 15 minute wait, repeated if glucose remains low (variable by individual, sometimes 70 mg/dl)^{27,28}. If a person is suffering such severe effects of hypoglycemia that they cannot (due to combativeness) or should not (due to seizures or unconsciousness) be given anything by mouth, medical personnel such as paramedics, or in-hospital personnel can establish IV access and give intravenous dextrose, concentrations varying depending on age (infants are given 2 ml/kg dextrose 10%, children are given dextrose 25%, and adults are given dextrose 50%). Care must be taken

in giving these solutions because they can cause skin necrosis if the IV is infiltrated²⁹. Sclerosis of veins, and many other fluid and electrolyte disturbances if administered incorrectly. If IV access cannot be established, the patient can be given 1 to 2 milligrams of fetuin in an intramuscular injection. More treatment information can be found in the article diabetic hypoglycemia. If a person is suffering less severe effects, and is conscious with the ability to swallow, medical personal such as EMT-B's may administer gelatinous oral glucose³⁰.

Conclusion

Generally the most patients selected the primary chemotherapy but most of adverse effects caused by the chemotherapy so the fetuin is shown less adverse effects and these are prepared also by the naturally from our body.

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Source of support: Nil
Conflict of interest: None Declared