Function of Collagens in Energy Metabolism and Metabolic Diseases

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Abstract

Living organisms use energy to maintain their life through metabolism, and there is a balance between energy and substrates in living organisms. Adipose, liver, muscle cells and pancreatic cells are the major tissues which involved in this process. Collagens are produced in most of these cells in response to complicated physiological changes. Defining the cellular sources of collagens in the normal and diseased states of the above metabolic tissues is thus critical to understanding metabolic disease. Under certain pathological conditions, the excess accumulation or collapse of collagens may disrupt normal cell-cell interactions, and cause the loss of tissue compliance or elasticity. Finally, these disruptions of collagens result in tissue dysfunction such as atherosclerosis of the blood vessels, pulmonary fibrosis, liver cirrhosis and fibrosis in other organs. This review will focus on the role of collagens in metabolic tissues, and attempt to summarize the function of collagens in energy metabolism.

Keywords: Hepatocytes; Liver cirrhosis; Atherosclerosis; Glycoproteins

Introduction

The main components of the interstitial matrix and the basement membrane in the extracellular region of animal tissue are referred to as the extracellular matrix (ECM). The ECM plays important roles in providing support and anchorage for cells, regulating intercellular communication, and storing a wide range of cellular growth factors [1]. Thus, the rapid and local growth factor-mediated activation of cellular functions are triggered by changes in physiological conditions, without de novo synthesis.

The ECM is tissue specific in quality and quantity. Components of the ECM are secreted from the intracellular region of resident cells via exocytosis. The main components of ECM are the interlocking mesh of fibrous proteins and glycosaminoglycans (GAGs). Furthermore, the main fibrous proteins are collagens, of which 29 types have been reported [1,2]. The functions of these proteins include protection and support, and forming connective tissue, tendons, bone matrices, and muscle fiber.

Collagen proteins are large and complex, with multiple distinct domains, and are highly conserved among different species. Almost all collagen proteins are glycoproteins, protein cores made in the rough endoplasmic reticulum, and posttranslationally modified by glycosyltransferases in the Golgi apparatus. After being secreted into the ECM as precursors via exocytosis, they need a complex processes such as the cleavage of N- and/or C-propeptides which occurs via highly specific proteinases and then become mature collagens [3].

Liver

As the largest gland in the body, liver performs many important tasks and impacts all body systems. In light of this face, hepatic dysfunction could result in widespread effects on virtually all other organ systems. Therefore, hepatocytes are considered the most important organ in metabolism in the body. They play key roles in synthesizing molecules, converting them into one another, and being transferred elsewhere to support homeostasis and regulate energy balances. The major metabolic functions of the liver were shown to be involved in the metabolism of major nutrients such as carbohydrates, fat and protein [4]. For all animals, the concentration of glucose in the blood has to be maintained within a narrow, normal range, and the liver is the main organ that controls it. Many different metabolic pathways and dozens of enzymes in hepatocytes elaborately regulate the blood levels of glucose. Actually, three important processes in carbohydrate metabolism, glycogenesis, glycogenolysis and gluconeogenesis all happen in the liver. Although fat metabolism also occurs in other tissues, it is carried out predominantly in the liver [5]. Additionally, excess carbohydrates and proteins are converted into fatty acids and triglycerides in the liver, which are then exported and stored in adipose tissue. Cholesterol, phospholipids and lipoproteins are also synthesized in liver [6].

The liver collagens work as a foundation for the cells and occupy less than 3% of the liver area. Normal liver cells are separated physically by different matrix compositions such as collagens I, III, IV and V. The interstitium and a basement membrane-like ECM contains Type I, III, IV, V, VI, XIV, XVII collagens, and some others proteoglycans [7,8]. In normal liver, Collagens plays a disproportionately important role in liver function in health and disease, although it only takes up a small percentage of the volume. Collagens provide architectural elements for the liver with basement membrane or other duct architecture. Also, collagens have mechanical roles like providing tensile strength and resilience, modulating diffusion and vascular flow, and regulating cell movement. Importantly, collagens can also regulate signaling molecules such as growth factors, serving as ligands, storage depots and receptors, via multiple complex interactions between matrix proteins with other signal molecules or among different matrix components [9].

There is no doubt that liver fibrosis and the subsequent cirrhosis is the most widespread and well-known disease related to the collagens in the liver. Liver fibrosis may be the result of viral activity, metabolic disorders, chemicals, or other liver infections. An imbalance between secretion and degradation in the collagens may result in liver fibrosis.
Although significant improvement has been made in understanding the process of fibrosis through the use of multiple complementary experimental model systems in the past years, especially within the past 5-10 years, the treatment options are still limited [10]. Liver fibrogenesis is a complex process and begins with an increase in cellular isoforms of fibronectin in the space of Disse, followed by an accumulation of fibrillar collagens (predominantly type I and III collagens). At the same time, other events including inflammatory cell infiltration, apoptosis of hepatocytes and proliferation of the major matrix-producing mesenchymal cells are occurring [11]. As fibrosis progresses, portal to central gradients are lost, and the new matrix becomes continuous. Finally, the quantity of collagens in the fibrotic liver is a nearly 10-fold increase compared to normal liver [9]. When fibrosis advances to cirrhosis, the architecture of normal liver is lost and the new matrix becomes increasingly stabilized and protease resistant. It results in liver dysfunction and portal hypertension and increasing risk of liver cancer [12].

**Adipose**

Obesity is becoming an increasingly global risk for humans, even among younger people. Obesity, along with some diseases like type II diabetes and cardiovascular disorder, has intensified the attention on the metabolic and physiologic roles of adipose tissue. As the key regulator of systemic energy homeostasis, adipose tissue has many important functions, such as being the site of redundant energy storage, production of adipokines for energy metabolism, thermal maintenance for the body, and a shock cushion for the organs. In adipose tissue, the collagens play crucial roles in maintaining the structural integrity of adipocytes and are pivotal for adipogenesis and whole tissue formation. In 1963, Napolitano et al. first reported observations of ECM structure in adipose tissue via electron microscopy [14]. Following that, Cinti et al. reported collagen fibrils surrounding adipose cells and capillaries during the development of fat organs in young rats in 1984 [15]. In 1998, other ECM proteins such as collagen IV, fibronectin and heparin sulphate proteoglycan, were found surrounding human adipocytes by immunohistochemistry [16]. Also, preadipocyte cell lines secrete type I-VI collagens during differentiation [17]. A number of reports show that there is highly expression of type VI in adipose tissue which affects the differentiation of preadipocytes [18-20]. Recent studies also show that type V collagen is highly expressed in adipose tissue (Figure 1). The knockdown Col5a3 gene is also found to inhibit greatly the differentiation of mouse preadipocytes cell line 3T3-L1. Surprisingly, there were no significant differences in adipose and weight between the Col5a3 knockout and WT mice. However, there was a significant reduction in dorsal skin of 10-day-old mice and the weights of mice when fed with high-fat diet. This finding indicates that there may be some compensation mechanism for the function of the α3(V) chain during the differentiation of preadipocytes in vivo, but loss of function in cell line or high-fat diet mice [21].

*Figure 1: The expression of α3(V) in mouse tissues (Modified from [22])*

Thus, collagens defects have been shown capable of having profound effects on adipocyte biology. Ablation of the cell surface matrix metalloproteinase MT1-MMP (MMP-14) has been shown to result in adipocytes unable to correctly remodel surrounding collagenous ECM, which in turn impairs adipocytic differentiation, yielding "mini-adipocytes" with diminished functional capacity and mice with a lipodystrophic phenotype [22]. Additionally, during obesity, ECM components are modified and associated with collagen deposition [23]. Similarly to liver, prolonged excess energy intake induces fibrous depots in adipose, and this fibrosis is the consequence of both the amount and composition of collagens. Thus, the accumulation of collagens in the fibrous areas of adipose tissue was used as a marker for adipose fibrosis [24,25]. Finally, ablation of collagen VI was found, which like the α3(V) collagen chain is expressed at highest levels in adipose tissue [26], has been shown to result in increased adipocyte cell size that correlates with enhanced adipocyte function and concomitant improvement in metabolic profile on an ob/ob background [20].
Pancreas and Islet

As an important glandular organ in the digestive and endocrine systems in vertebrates, the pancreas produces several important hormones including insulin, glucagon and somatostatin which circulate in the blood to regulate glucose homeostasis. In fact, all of above hormones are secreted by the "micro-organs" islets in pancreas. Mouse islets are composed of insulin-secreting β-cells (around 60-80%), glucagon-secreting α-cells (15-20%), somatostatin-producing δ-cells (<10%) and other cells (<1%) [27]. The ECM has been shown to affect strongly many aspects of β-cell function, including motility [28], survival [29], proliferation and differentiation [30]. Several other reports showed that matrix interactions can also influence insulin function [31,32]. And other current other reports have demonstrated that islets survival and function were much better when cultured on ECM-derived substrates containing collagens [33-35]. In collagen type I hydrogels, the addition of collagen type IV and laminin increased islet insulin secretion [36]. Another study demonstrated that human islet adhesion, survival, and functionality, such as structural integrity, insulin expression and release, and glucose metabolism are all affected by the various ECM components including collagens I and IV [37]. Consistent with all of these findings, α3 (V) chains play an important role in islet development, proliferation and function. And which suggests that α1(V)α2(V)α3(V) heterotrimers may enhance the survival and function of primary β-cells during culturing and upon encapsulation in gel environments for transplantation [21].

The pancreas can also show fibrosis pathology that is characterized by stromal expansion and deposition of collagens. Pancreatic fibrosis underlies many endocrine diseases including pancreatic cancer, chronic pancreatitis, and type 2 diabetes mellitus. Although the detailed mechanisms are not understood clearly, these facts indicate that collagens-dependent EGFR signaling may be involved in regulation of pancreatic fibrogenesis in vivo [38]. Many studies demonstrated that diabetic nephropathy is characterized by abnormal collagens deposition in renal pathology, with the molecular mechanism being the MMP-mediated breakdown and turnover of ECM in mesangium and glomerulus cells [39]. Interestingly, other studies demonstrated that high glucose can induce collagens synthesis, and accelerate metabolic tissues like pancreas and liver fibrosis [40,41]. Compared with islets in WT mice, the relative β cell area was significantly reduced in Col5a3−/− mice, mostly due to reduced islet numbers. Furthermore, the overall weights of Col5a3−/− pancreases were also less than those of wild-type pancreases, contributing to reduced Col5a3−/− β cell mass, and resulting in the defects of insulin secretion in Col5a3−/− mice [21]. These observations may be helpful in developing an appropriate therapeutic strategy in diabetic conditions.

Muscle

Skeleton muscle and tendon

The ECM in skeletal muscle is organized in different levels, and collagens are the most abundant structural components of skeletal muscle ECM. 1% to 2% of muscle tissue and 6% of the weight of muscles are collagens [42]. In addition to the collagens, the ECM in skeleton muscle includes a variety of other non-collagen glycol proteins such as laminins, nidogens and perlecan.

The treatment of diabetes, obesity and heart disease benefit from exercise, and it is a normal and healthy way of energy expenditure in humans. Collagens play critical roles in force transmission and tissue structure maintenance in tendons, bone and muscle. It is well known that the contractile filaments in skeletal muscle are important to force development, and the tendon tissue transform this developed force from the muscle to the bone [43,44]. In addition, collagens also play a role in the skeleton muscle development. It is clear that muscle development requires collagen proteins to ensure myoblast migration, proliferation, and differentiation [45]. Recently, researchers administrated that muscle collagen synthesis increased almost 4-fold in response to bouts of heavy resistance exercise [45,46]. In conclusion, the ECM of both tendon and skeletal muscle tissue reacts dynamically to mechanical loading and this increases collagen synthesis, and the high expression of collagen synthesis result in the increased load from tendons and muscle.

Smooth muscle cells and cardiac muscle cells

Vascular smooth muscle cells (VSMCs) normally reside in the media of the artery, lined with endothelial cells, and are surrounded by a specialized thin sheet-like structure of extracellular matrix components, including collagens types I, III, IV and V et al. [47,48]. A major function of the vascular SMCs is to synthesize and organize the unique ECM proteins responsible for the mechanical properties of the large vessels during angiogenesis. Hence, the ability to produce ECM can be considered a defining phenotype for the differentiation of SMCs and the form of angiogenesis [49]. Production of a functional matrix in SMCs requires the coordinated expression, modification, process of the ECM proteins, and some others signals such as PDGFβ, EDG1 and TGF-β that are involved in the processing and assembly of most ECM networks, including basement membranes, elastic fibers, and large proteoglycan matrices.

Additionally, the roles of collagens in heart, especially in the heart remodeling, have attracted enormous attention recently. The components of cardiac ECM are composed of fibrous proteins and glycosaminoglycans (GAGs). Fibrous proteins such as collagen and elastin serve as reinforcements for the myocardium. GAGs such as glycoproteins and proteoglycans function as the space-filling concrete in the heart. The mechanical support for pumping blood in the heart is also provided by Collagens [50]. The concept that ECM turnover occurs during cardiac remodeling is a well-accepted paradigm. The increases of collagens were synthesized and deposited during the cardiac remodeling [51]. A number of muscle and related pathologies involves changes in matrix properties. Beyond the myocardial infarctions mentioned above, the abnormality ECM proteins also result in the vascular diseases such as type V and IV collagens, laminin and perlecambased atherosclerosis [47,48]. Type II collagen-induced Rheumatoid arthritis [52], fibrillin-1-induced Marfan syndrome, type I collagen-Osteogenesis and elastin-supravalvular aortic stenosis [53]. In tendons, the tendonosis occurs when the fibrous material collagens in a tendon begins to degenerate. This may occur as the result of injury. The tendon becomes tangled, weak and jelly-like when collagen degenerates. Additionally, muscular dystrophies are also associated with changes in matrix [54]. The summary of collagens-related metabolic disease in above metabolic tissues was shown in Table 1.

Cell signal pathway

The diverse array of collagens not only provide the physical structure of the cell, but also various biological functions largely through them to bind many other interacting partners such as growth factors, other ECM proteins, signal receptors, and adhesion molecules.
like integrins. The collagens perform profound effects on cell fate and behaviors via interacting with the surface receptors and growth factors and then transduce to cytoplasmic signal pathways [55].

| Collagens | Distribution | Function | Metabolic disease(s) |
|-----------|--------------|----------|---------------------|
| Type I    | Most common of the collagens, distributed in all tissues, even cartilage. | Structural components for body, essential for the tensile strength of bone. | Atherosclerosis [69]; fibrotic diseases in many tissues including liver [11] and adipose [28] etc.; Increased in diabetic nephropathy [70] but decreased in T1DM [71]. |
| Type III  | Dominant collagen type of granulation, muscle and artery wall. | Crucial for collagen I fibrillogenesis and for normal cardiovascular development. | Vascular Ehlers-Danlos syndrome [72]; Atherosclerosis [69]; fibrotic diseases in many tissues including liver [11] and adipose [28]; Increased in T2DM [73] and T1DM [71]. |
| Type IV   | Structural component of basement membrane | Associated with angiogenesis. | Increased in diabetic nephropathy [74,75]; Retinopathy [76]; Liver fibrosis [77]. |
| Type V    | Structural component of basement High expression in muscle, adipose and islet. | Interact with type I collagen, inhibits endothelial cell adhesion and proliferation. | Atherosclerosis [48,69]; Glucose homeostasis and diabetes [21]; Liver fibrosis [9]. |
| Type VI   | Dominant structural component of connective tissues like vessels, liver, adipose and muscle. | Major structural component of microfibrils. | Atherosclerosis [69]; Metabolic dysregulation and adipose fibrosis [20]; Liver fibrosis [78] and myosclerosis myopathy [79]. |
| Type VIII | Structural component of ECM like sclera and vasculature. | Stabilization of membranes, angiogenesis and interacts with ECMs | Atherosclerosis [80]. |
| Type XII  | Structural component of connective tissue e.g. skin. | Interacts with other matrix components. | Diabetic retinopathy [81]. |
| Type XIV  | Structural component of connective tissue like blood vessels. | Interacts with other matrix components. | Diabetic retinopathy [81]. Liver fibrosis [8]. |
| Type XVIII | Structural component of basement membrane. | Inhibition angiogenesis and tumor growth. | Liver fibrosis [82]. |

Table 1: The roles of main ECM molecules in metabolic tissues

The collagens can collaborate with their receptor integrins, growth factor receptors and intracellular signals to regulate gene expression associated with metabolic cell growth, differentiation, survival and glucose uptake. Integrins can recognize and binds to the Arg-Gly-Asp (RGD) motif in ECM proteins like fibronecrtin, and some collagens [56]. This binding results in integrins conformation and outside-in integrin activation, the outside-in activation propagates signals to the cytoplasm [57]. A large body of evidence now indicates that collagens/integrin pathways can collaborate to activate a non-receptor tyrosine kinase focal adhesion kinase (FAK) and the Ras-MAPK-ERKs pathway [58,59]. FAK activation leads to the recruitment of PI3 kinase to focal adhesion, and results in activation of Akt, then activate the GLUT4 translocate to plasma membrane and regulate the glucose uptake and metabolism. In addition, ECM/integrin can also regulate islet cell survival and function via PI3K/Akt signaling pathways [60]. Our data also showed that decrease of phospho-Akt and less GLUT4 translocated to the plasma membrane in adipose and muscle tissues of Col5a3−/− mice compared to WT mice [21]. Downregulation of Akt and phospho-Akt was also found, along with a decrease in islet mass in the islets of Col5a3−/− mice. This indicates that type V collagen is involved in the activation of integrin-mediated FAK-PI3K-Akt pathway. Furthermore, collagens/integrins pathway can also reorganize the plasma membrane into highly ordered specific structure-caveolae, which effectively concentrates the multi-protein signaling complex like GLUT4, IGFR, EGFR and FAK. Any changes in caveolae can effectively turn off the entire signaling pathway [61]. In fact, dysstructure of caveolae like Caveolin-1 and 3 knockout mice, showed insulin resistance [62,63]. The Ras-MAPK-ERKs pathway play crucial roles in most of cell growth and proliferation include metabolic tissue cells. Our recent unpublished data also show that type V collagens can interact with Glypican-1 and regulate breast tumor growth via the Ras-MAPK-ERKs pathway.

Aside from integrins, discoidin domain receptors (DDR1 and DDR2) are another types of receptors for ECM collagens. DDR1 and DDR2 are unique members of the family of receptor tyrosine kinase (RTK) in that they bind to and are activated by native triple-helical collagen [64,65]. Unlike most other RTKs, DDR1 and DDR2 are activated by various types of collagens but not by growth factors. DDR1 is activated by most collagens like type I to type IV, and type VIII, while DDR2 is activated by fibrillar collagens, including type I, II and X [66,67]. Interaction of the DDRs with collagens leads to receptor autophosphorylation, and then to the activation the downstream signal molecular pathways, including PI3K, NFκB, ShcA and P38 etc. pathways, to regulate cell differentiation, migration, and metabolism. A number of human diseases, including fibrotic diseases of the liver and atherosclerosis are associated with DDRs [66]. Additionally, DDR2 is downregulated during the early phase of adipogenesis, and its overexpression leads to insulin resistance in 3T3-L1 adipocytes [68].

Conclusions

Metabolic diseases continue to be a major health challenge of pandemic proportion in the world. They can be caused by lifestyle or...
genetic variants, leading to the dysfunction of energy balance through a complex pathophysiological process. The ECM remodeling and tissue destruction are required during these complex processes. Lots of component increases, decreases or modifications are involved in ECM remodeling, especially collagens remodeling. With the current level of research and increasing understanding of the function of collagens, there is hope that better medications will emerge to control complex metabolic diseases.

It is well-known that extracellular signals including growth factors and cytokines bind to specific receptors on the surface of their target cells. Recently, more and more findings were reported that collagen not only builds the main structural components among the cells, but also covalently anchors to the plasma membrane of the cells to enhance the efficient binding between the cytokines and their specific receptors, thereby modulating their mitogenic and angiogenic effects on different types of cells. Obviously, the ECM components, especially the collagens, will be recognized as the key regulators in cell physiological activities in future. Another way to regulate the effects of growth factors and cytokines will provide an alternative therapeutic target to regulate the cellular growth, proliferation, and cellular differentiation. Additionally, it is well-known that most of collagens are high-modified proteins, and these modifications of collagens are required for their function. And some of our unpublished data showed that some new modifications occurred in an extracellular region specific for the ECM components. This indicates that ECM may have a new protein modification system different from what is known so far about the cellular Golgi and endoplasmic reticulum systems.

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