Chapter

Vascularisation of Skeletal Muscle

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Abstract

Skeletal muscle is mainly involved in physical activity and movement, which requires a large amount of glucose, fatty acids, and oxygen. These materials are supplied by blood vessels and incorporated into the muscle fiber through the cell membrane. In contrast, metabolic waste is discarded outside the cell membrane and removed by blood vessels. The formation of a functional, integrated vascular network is a fundamental process in the growth and maintenance of skeletal muscle. On the other hand, vascularization is one of the main central components in skeletal muscle regeneration. In order for regeneration to occur, blood vessels must invade the transplanted muscle. This is confirmed by the fact that muscle regeneration occurred from the outside of the muscle bundle toward the inner regions. In fact, it is likely that capillary formation is a key process to start muscle regeneration. Thus, vascularization activates muscle regeneration, and a decrease in vascularization could lead to disruption the process of muscle regeneration. Also, a better understanding of vascularization of skeletal muscle necessary for the successful formation of collateral arteries and recovery of injured skeletal muscle may lead to more successful strategies for skeletal muscle regeneration and engineering. So, in this chapter, we want to review vascularization in skeletal muscle.

Keywords: vascularization, angiogenesis, arteriogenesis, skeletal muscle

1. Introduction

Vascularization of skeletal muscle occurs by four distinct processes: vasculogenesis, angiogenesis, arteriogenesis, and lymphogenesis.

1.1 Vasculogenesis

The fundamental biological phenomenon of new vessel formation is one enormous complexity, and has excited the interest of scientific workers for many years. Vasculogenesis describes the formation of the primitive network of blood vessel in the embryo from undifferentiated precursor cells (angioblasts), and the differentiation of angioblasts to endothelial cell. This is the initial step to blood vessel formation de novo. To form a new vessel, angioblasts proliferate and join up with primary capillary plexus. The endothelial cell grid manufactured by vasculogenesis then serves as an angiogenesis framework [1]. After primary capillary plexus formation, it is altered by the sprouting and branching of new vessels from pre-existing ones. The majority of work on skeletal muscle capillaries has focused on angiogenesis [1].

1.2 Angiogenesis

Angiogenesis and inflammation are critical to the process of muscle regeneration, but the complex interactions between these multiple cell types are poorly understood [2]. Most normal angiogenesis occurs in the embryo where it establishes the primary vascular tree as well as an adequate vasculature for growing and developing skeletal muscles. Angiogenesis involves the growth of new capillaries from existing blood vessels within the skeletal muscle and occurs in the adult during the ovarian cycle and in physiological repair processes such as wound healing. However, very little turnover of endothelial cells occurs in the adult vasculature. In order for new blood vessel sprouts to form, as previously described by Papetti et al. [1], mural cells (pericytes) must first be removed from the branching vessel. Endothelial cell basement membrane and extracellular matrix is then degraded and remodeled by specific proteases such as matrix metalloproteinase (MMPs), and the new matrix synthesized by stromal cells is then laid down. This new matrix, coupled with soluble growth factors, fosters the migration and proliferation of endothelial cells. After sufficient endothelial cell division has occurred, endothelial cells arrest in a monolayer and form a tube-like structure. Mural cells (pericytes in the microvasculature and smooth muscle cells in larger vessels) are recruited to the abluminal surface of the endothelium, and vessels uncovered by pericytes regress. Blood flow is then established in the new vessel [1]. Angiogenesis in the skeletal muscle can occur by two primary mechanisms: sprouting and intussusception.

1.2.1 Sprouting angiogenesis

Sprouting in angiogenesis refers to activated endothelial cells diverging from the existing vasculature, continuing through the encompassing matrix to form a cord-like structure (see **Figure 1**). The endothelial cell cord is changed into a tube and sticks to the extracellular matrix. It should be noted that the newly formed tube must reenter the capillary network via joining with another capillary or venule to become a functional capillary. Newly formed capillary in the beginning is leaky, but it blossoms to that of the original capillary when pericytes surround completely the endothelial cells. Like intussusception, sprouting needs to activate endothelial cells [3].

1.2.2 Capillary intussusceptions

Intussusceptions point to the process by which a mature capillary is divided into two separate capillaries from within, by the formation of a pillar-like structure or longitudinal divide on the luminal side of the capillary (**Figure 2**). Activated endothelial cells extend intraluminally, effectively forming two tubes through which blood can pass. Previous studies confirmed that intussusception is a main method of capillary formation during development. Angiogenic responses were differential in vivo. In this case, it is mentioned that shear forces acting on capillaries may preferentially increase capillarity through intussusception [3]. On the other hand, as shown in **Figure 3**, overload by activation of MMPs and VEGF leads to angiogenesis via sprouting.

1.3 Arteriogenesis

Arteriogenesis, formerly regarded as a variant of angiogenesis, is a relatively new term that was introduced to distinguish it from other mechanisms of vascular growth, such as angiogenesis and vasculogenesis. Vasculogenesis describes the

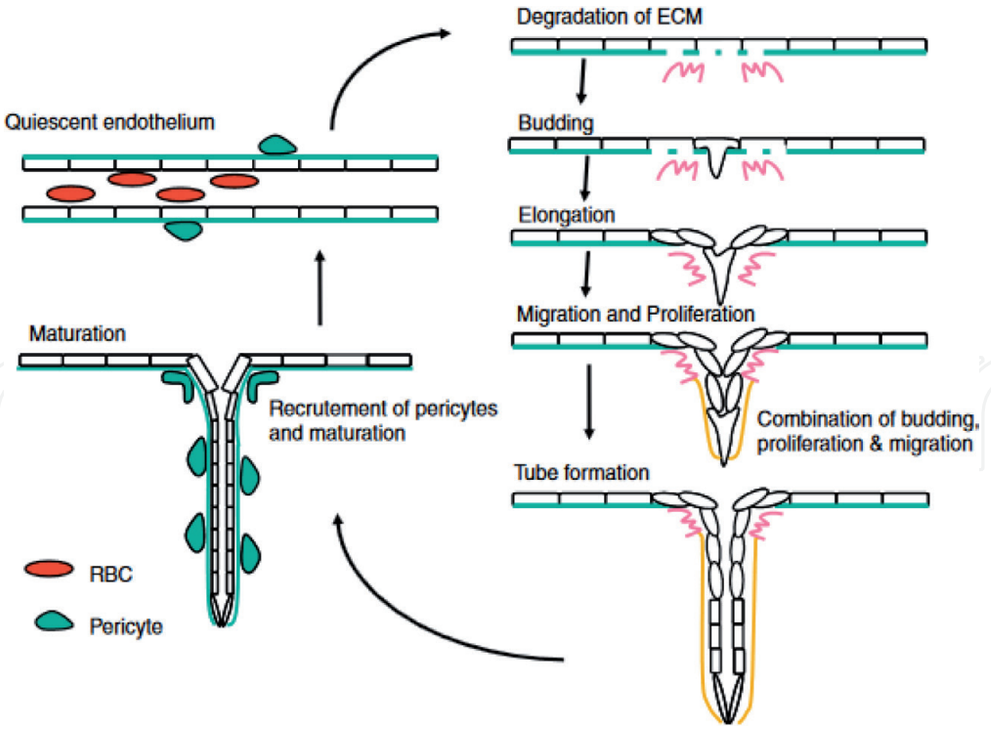

Figure 1.
Schematic representation of sprouting angiogenesis [4].

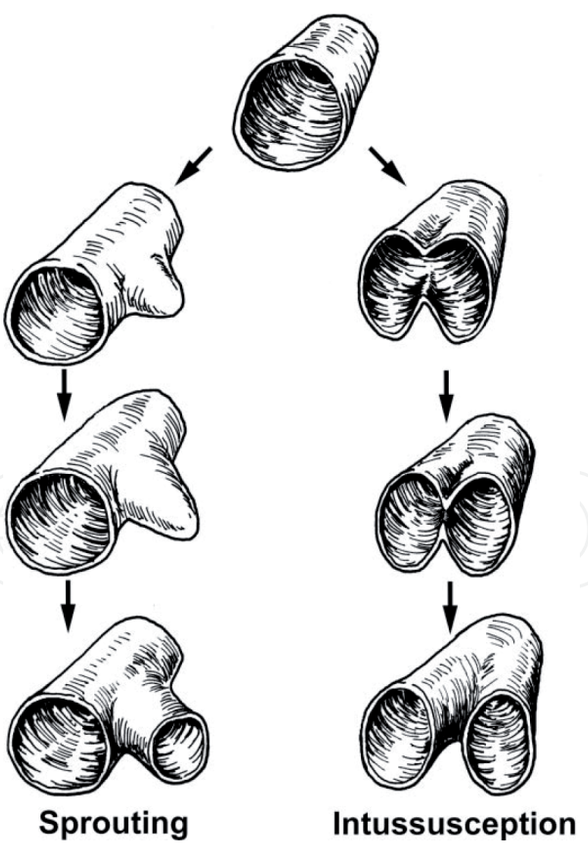

Figure 2.
Angiogenesis occurs by the processes of intussusception and sprouting.

embryonic development of blood vessels from angioblasts, and angiogenesis is the formation of new capillaries by sprouting and intussusception from pre-existent capillaries. But, arteriogenesis describes the formation of mature arteries from pre-existent interconnecting arterioles after an arterial occlusion. Arteriogenesis pointed

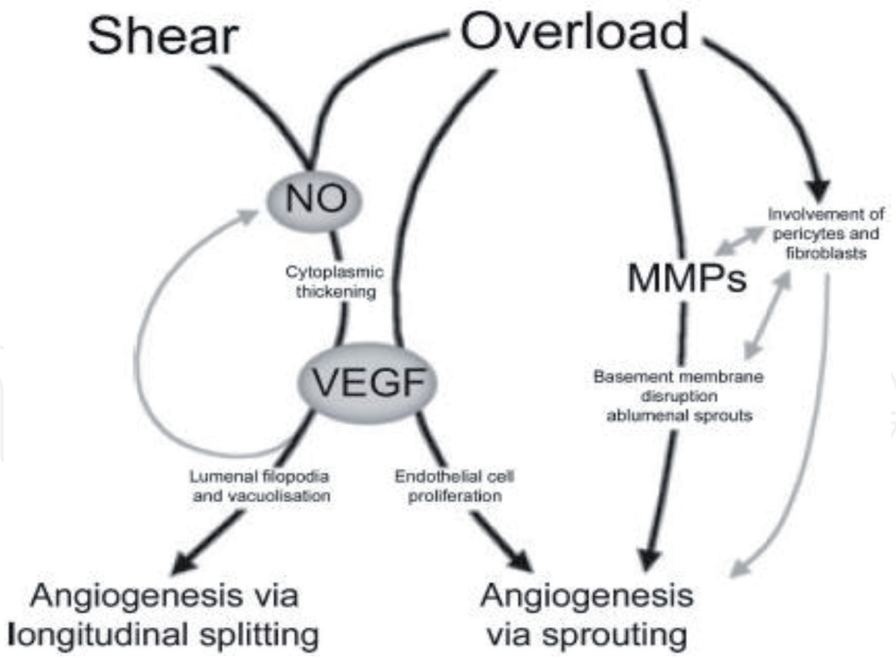

Figure 3.
Differential angiogenic responses in vivo [5].

to the enlargement of existing arterial vessels [6]. This enlargement indicates an increase in the caliber (diameter) and wall dimensions, resulting in a larger vessel. It is similar to angiogenesis in some features, but the pathways make it different [7].

Angiogenesis occurs under hypoxia/ischemia condition, which leads to the activation of the transcription factor HIF (hypoxia-inducible factor); in contrast, arteriogenesis is activated in an environment of normoxia [8].

Growth of arterioles in skeletal muscle has been documented during development.

Transformation of pericytes into smooth muscle cells and/or apposition of mesenchymal cells, most likely fibroblasts, to the abluminal surface of capillaries, followed by their gradual change into pericytes or smooth muscle cells lead to the growth of arteriolar known as "arteriolarization" [9]. Arteriolar growth accompanied rather than followed capillary growth.

1.4 Lymphogenesis

Lymphatic vessels act in close relation with blood vessels. The formed lymph fluid is transported via initial lymphatic capillaries to collecting vessels, to lymph nodes, and finally back to the blood [10]. Hyperemia-induced increased filtration of skeletal muscle (during activity), promotes hydrostatic and colloid osmotic pressure and addresses the need for increased lymph flow to maintain optimal conditions in the muscle. It is clear that exercise increases skeletal muscle lymph flow significantly in both animals [11] and humans [12], especially at the beginning of exercise. Studies showed that skeletal muscles contain small capillary-sized lymphatic vessels, which are located next to blood capillaries between muscle fibers but are much fewer in number.

2. Stimulators of vascularization in skeletal muscle

The studies showed that hypoxia, shear stress, adenosine, and muscle stretch are the most important stimulators of the angiogenesis process which are more fully described.

2.1 Hypoxia

Tissue hypoxia is thought to upregulate a series of local factors that contribute to angiogenesis. The status of tissue oxygenation determines blood vessels to undergo angiogenesis or stay quiescent. Accumulation of hypoxia-inducible factor (HIF)-α under hypoxia condition triggers tissue angiogenesis. HIF-α plays a pivotal role in the transcriptional activation of genes encoding angiogenic factors. Briefly, as previously described by Fong et al. [13], HIF-α abundance is negatively regulated by a subfamily of deoxygenates referred to as prolyl hydroxylase domain-containing proteins (PHDs), which use O_2 as a substrate to hydroxylate HIF-α subunits and hence tag them for rapid degradation (**Figure 4**). Under hypoxic conditions, HIF-α subunits accumulate due to reduced hydroxylation efficiency and form transcriptionally active heterodimers with HIF-1β to activate the expression of angiogenic factors and other proteins important for cellular adaptation to hypoxia. Angiogenesis is regulated by a combination of at least two different mechanisms. The paracrine mechanism is mediated by nonendothelial expression of angiogenic factors such as vascular endothelial growth factor (VEGF)-A, which in turn interacts with endothelial cell surface receptors to initiate angiogenic activities. In the autocrine mechanism, endothelial cells themselves are induced to express VEGF-A, which collaborate with the paracrine mechanism to support angiogenesis and protect vascular integrity [13].

2.2 Shear stress

Relatively little is known about the importance of mechanical forces and the mechanisms of their transduction during the growth of vessels in skeletal muscle [14]. Repeated muscle contractions alter the local microcirculatory hemodynamics by dilatation of arterioles leading to increases in capillary flow velocity, shear stress (defined as shear stress = blood viscosity × (8 × mean flow velocity)/vessel diameter) [15] and, potentially, pressure. Capillary growth in response to shear stress proceeds by division of the lumen by endothelial cell protrusion and vessel splitting, without the requirement for disturbance and breakdown of the basement membrane [14].

According to the mechanotransduction hypothesis, shear-induced endothelial cell deformation, cytoskeletal perturbations, and increasing tension at the focal adhesion attachment sites activate the integrins, generating intracellular signals that include transcription of genes involved in angiogenesis [15].

It is known that increased shear stress in endothelial cell cultures leads to an increase in protein expression of VEGF receptor 2 (Flk-1) [16]. Today it is clear that shear stress releases NO and increases VEGF and its receptor 2 expression during the initiation of endothelial cell proliferation and angiogenesis [14].

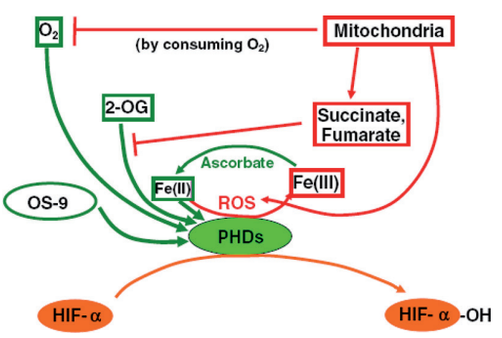

Figure 4.
Regulatory mechanisms of PHD hydroxylase activities. Factors or processes with positive effects on PHD hydroxylase activities are shown in green, whereas those with inhibitory effects are shown in red [13].

2.3 Adenosine

Of the major metabolites produced and released by exercising skeletal muscle, adenosine has received the greatest attention as an angiogenic factor. Adenosine is generated as ATP is catabolized when energy demands increase or oxygen supply decreases [17]. Feoktistov et al. demonstrated that stimulation of adenosine A_2B receptors upregulates the angiogenic factors VEGF and IL-8 in human endothelial cells under normoxic conditions [18]. Studies in other cell culture models conducted under normoxic conditions have also indicated that adenosine upregulates proangiogenic and downregulates antiangiogenic factors [19]. Remarkably, chronic infusion of adenosine induced neovascularisation in the skeletal muscle and the heart muscle [20].

2.4 Muscle stretch and exercise

Original studies demonstrated that stretch of cells promotes VEGF (mRNA and protein), which leads to enhanced endothelial cell migration and tube formation, and activates MT1-MMP, and upregulates Ang-2 and Tie-2 expression. Stretch also causes deformation of the extracellular matrix, and may result in the release of matrix-bound growth factors, that then can bind to and activate the surrounding cells. Furthermore, stretch induces tensional forces that initiate mechanotransduction signaling pathways through activation of integrin receptors [15].

When specific muscles are exercise trained, there can be an increase in flow capacity and an expected increase in the caliber of the large conduit vessels [21]. In this regard, Hounker et al. demonstrated that the subclavian arteries of the dominant arms of elite tennis players exhibited larger diameters than control group arteries [22]. Also, increased diameters of the femoral arteries were observed in elite cyclists, whereas decreases were observed with paraplegia compared with corresponding controls [21]. This increase in flow capacity to the major muscle groups of highly trained individuals could contribute to the greater exercise capacity exhibited by these individuals. Capillarity in active skeletal muscle is significantly increased by endurance exercise training although the increase in the heart muscle is less well established.

In this regard, laboratory studies indicate muscle mass loss [23], increased number of fast-twitch fibers, decreased slow-twitch fibers [24], and restriction of skeletal muscle blood flow in humans [25] and animals [26] after myocardial infarction. In addition, systemic blood flow in the skeletal muscle of mice with heart failure decreases at rest and during physical activity [27]. Experimental studies at the capillary level show that capillary density parameters [28] and capillary/fiber ratio (CF ratio) decrease following myocardial infarction. On the other hand, at the arteriole level, the arteriole tonic sympathetic vasoconstriction activity increases that decreases the arteriolar diameter and elasticity capacity [29].

A remaining question is what signaling cascade within the muscle fibers decodes muscle contractile activity signals in regulating VEGF expression. Mechanistically, the functional role of PGC-1α in exercise-induced VEGF expression and angiogenesis is dependent on the upstream p38 mitogen-activated protein kinase (p38γ MAPK) [30] and the downstream ERRα [31]. Interestingly, transgenic mice with muscle-specific expression of an inactive form of 5′-adenosine monophosphate-activated protein kinase (AMPK) have lower capillarity compared with the wild-type littermates, but have normal-induced angiogenesis in response to voluntary running exercise [32, 33].

The importance of other growth factor pathways remains to be elucidated. Although several signaling pathways have been identified (**Figure 5**), significant

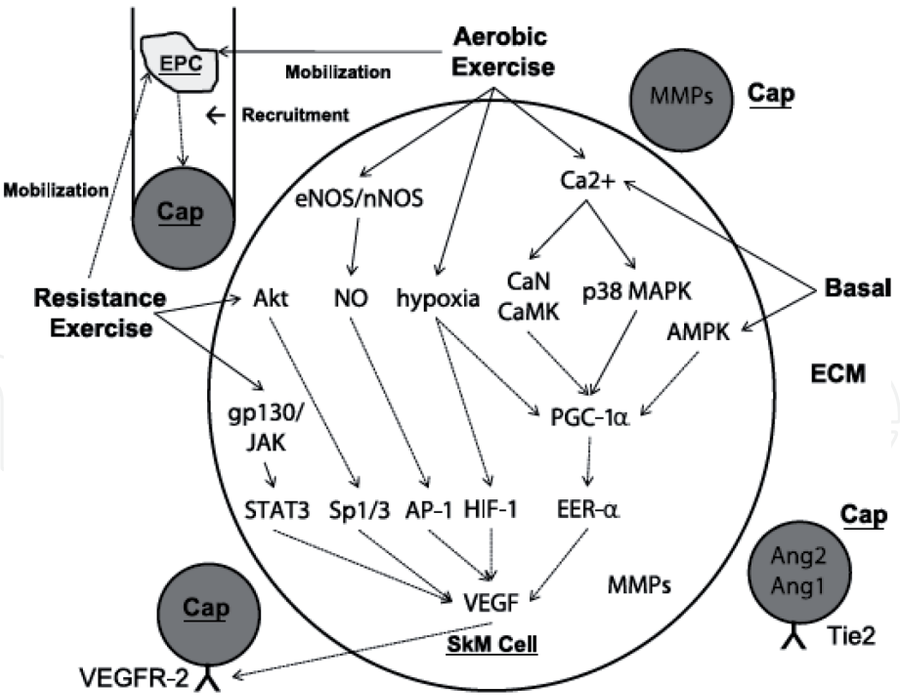

Figure 5.
Proposed model including intracellular signaling and growth factor regulation in skeletal muscle. Solid lines (—) are established pathways. Dashed lines (- -) are hypothesized pathways [34].

work remains on understanding the intracellular signaling pathways and transcription factors involved in basal- and exercise-induced angiogenesis [34].

It is well known that the vascularization of skeletal muscle adapts to various physiological and pathological conditions such as fiber type, gender, aging, obesity, and diabetes.

3. Fiber type and vascularization

The skeletal muscle is composed of a combination of different muscle fiber types: I, IIa, and IId/x. Fast- and slow-twitch fibers have different phenotypes with Type I fibers demonstrating the greatest and Type IId/x fibers demonstrating the least mitochondrial volume and capillarization.

It has been confirmed that muscle fibers with a high oxidative potential are related to a denser capillary network. This would mean that highly oxidative fibers require a higher rate of oxygen delivery than nonoxidative fibers; therefore, they must be better supplied with a capillary network [35].

Capillary density did not always correlate with oxidative capacity or maximal blood flow.

Previous studies demonstrated that after triiodothyronine administration, rat soleus and white area of the medial head of gastrocnemius muscle capillarity are promoted, whereas the oxidative capacity increased in the soleus only [36]. Therefore, in strait skeletal muscles, oxidative capacity is not the only factor that determines capillarity. On the other hand, it is likely that anaerobic waste accumulation stimulates vascularization in glycolytic regions of rat skeletal muscles, which is not accompanied by changes in oxidative metabolism [37, 38].

Already, at first, some researchers showed that capillary density is not related to the type of muscles, but hypothesized that the mean number of capillary profiles around a fiber for red and white muscles due to the size of the fiber. Sullivan and Pitman confirmed that capillaries around glycolytic fibers must supply blood

stream to a greater volume of a muscle fiber than capillaries serving oxidative fibers [39]. In this regard, independent of fiber type in human muscles, there is a positive correlation between local capillary-to-fiber ratio (LCFR) and fiber area [40].

Cebasek and co-workers showed that the length of capillaries per unit fiber length was larger in Soleus (Slow muscle) than in Extensor Digitorum Longus (EDL, Fast muscle) muscle. On the other hand, these researchers showed that capillary length per unit fiber volume was larger in EDL muscle. There was no difference in the length of capillaries per unit fiber surface area between the two muscles. Oxidative and glycolytic fibers differ in the length of capillaries per unit fiber surface area. This parameter probably reflects the oxidative capacity of muscle fibers [41].

Ranjbar et al. showed that the pattern of vascularization in response to exercise training is different between fast- and slow-twitch muscles. We showed that the 10-week exercise training significantly increased capillary density and capillary-to-fiber ratio ($P < 0.05$) in slow-twitch muscle, but did not change fast-twitch muscle capillary density and capillary-to-fiber ratio. Furthermore, arteriolar density in fast-twitch muscle increased remarkably ($P < 0.05$) in response to training, but slow-twitch muscle arteriolar density did not change in response to exercise in chronic heart failure rats. HIF-1 increased ($P < 0.01$) but VEGF and FGF-2 mRNA did not change in slow-twitch muscle after training. In fast-twitch muscle, HIF-1 mRNA increased ($P < 0.05$), and VEGF and angiostatin decreased ($P < 0.01$) significantly after training. We concluded that endurance training ameliorates fast- and slow-twitch muscle revascularization nonuniformly in chronic heart failure rats by increasing capillary density in slow-twitch muscle and arteriolar density in fast-twitch muscle. The difference in revascularization at slow- and fast-twitch muscles may be induced by the difference in angiogenic and angiostatic gene expression response to endurance training [42].

In this regard, we showed that smaller arterioles decreased in cardiac after myocardial infarction. Aerobic training and l-arginine increased the number of cardiac arterioles with 11–25 and 26–50 μm diameters parallel to TGF-β overexpression. In gastrocnemius muscle, the number of arterioles/mm2 was only increased in the 11–25 μm in response to training with and without l-rginine parallel to angiostatin downregulation. Soleus arteriolar density with different sizes was not different between experimental groups. Results showed that 10 weeks aerobic exercise training and l-arginine supplementation promotes arteriogenesis of heart and gastrocnemius muscles parallel to overexpression of TGF-β and downregulation of angiostatin in myocardial infarction rats [43].

On the other hand, Panisello et al. showed that SO fibers are more sensitive to intermittent hypobaric hypoxia than both fast fiber types [44]. Furthermore, Murakami et al. showed that capillary-to-fiber ratio, Microvessel diameter, expression level of VEGF, and number of microvessels in the soleus were significantly higher than those in the EDL muscle [45].

In conclusion, capillary supply is evidently well adapted to different muscle fiber types; consequently, an average capillary supply of heterogeneous muscle depends on the muscle composition.

4. Gender

Numerous studies have reported on the physiological differences among genders, but the effect of gender on neovascularization of skeletal muscle is not yet clear, and research in this field is limited.

Robbins et al. showed that men had a greater capillary-to-fiber ratio than women. However, capillary density per square millimeter was not different between men and women [46]. Also, Kyriakides et al. showed that gender does not influence angiogenesis and arteriogenesis in the rabbit model of chronic hind limb ischemia [47]. Opposite to these findings, Keteyian et al. showed that capillary density at baseline was significantly greater in men (1.42 ± 0.08 endothelial cells × fiber $^{-1}$) than in women (1.12 ± 0.03 endothelial cells × fiber^{-1}) [48].

5. Aging

Aging effects on the structure and function of skeletal muscles have been intensely studied for decades; however, age-related changes in skeletal muscle capillarity still remain controversial [49].

Studies in both humans and animals have also produced conflicting results in skeletal muscle capillarity, with results in increases [50, 51], decreases [52, 53], or no change [54] in muscle capillaries with advancing age. These inconsistent reports could be due to a difference in factors, such as muscle type, fiber-type composition, and how this composition changes during aging, as well as to differences in subject activity levels and gender [55].

In general, it is believed that aging reduces the ability of an organism to respond to different types of stress [56]. For example, the angiogenic response to hind limb ischemia is impaired in aged compared with young mice [57, 58]. Researchers showed reduced angiogenic capacity in skeletal muscle with aging. Reduction of muscular oxidative capacity attainable through training in elderly people is related to the reduction in fitness that typically occurs in this population. The decrease in muscle blood flow in the aging period is related to altered reactivity of resistance arteries and arterioles, with impairment of both vasodilator and vasoconstrictor responses as a consequence of endothelial dysfunction [21]. Whilst aging and sedentary life style both lead to structural and functional impairment in skeletal muscle blood supply network, it is not yet clear whether impaired angiogenesis is an indirect response to reduced flow capacity. It is clear that reduction of VEGF secretion with maintaining of the ability to respond to exogenous cytokines is due to endothelial cell dysfunction with aging [21].

6. Obesity

Obesity is a major health problem in the United States and many other developed countries. Several lines of evidence have demonstrated that the capillary density and oxidative capacity appear to be more strongly correlated with insulin sensitivity and body fatness than the prevalence of a specific fiber type [59].

Increasing adiposity is associated with lower skeletal muscle oxidative capacity and capillarization. Plasma insulin elevation does not result in insulin increment in the interstitial space concentration between the capillary and muscle fiber [60], suggesting that a limit may exist in the diffusional conductance of insulin in skeletal muscle.

Research studies have shown that there are associations between lower insulin action and a lower muscle capillary-to-fiber area ratio in obese muscle. It is likely that compared with lean individual, a delayed transport of insulin over the capillary wall may be attributed to lower skeletal muscle capillary density in obese individuals [61].

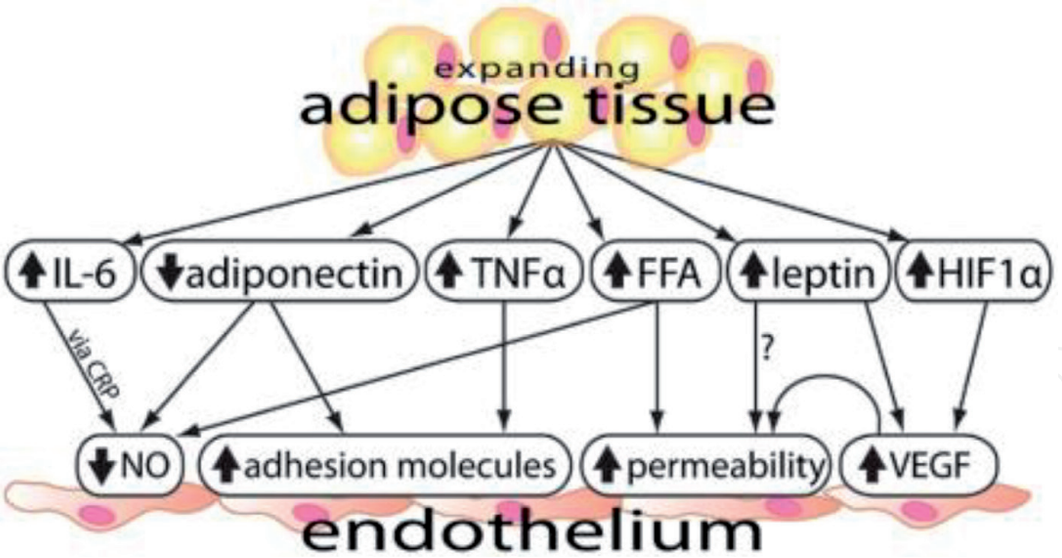

Figure 6.
Interactions between expanding adipose tissue and the endothelium [64].

In this regard, researchers showed that VEGF circulation, myocardial VEGF expression, and VEGF receptor 2 [kinase insert domain-containing receptor (KDR) human/Flk-1 murine analog] were not different between lean and obese individuals, but VEGF receptor 1 (Flt-1) is lower in obese compared with lean Zucker rats [62, 63]. Gavin et al. showed lower capillary density but no difference in VEGF expression in obese versus lean young skeletal muscle in humans [61].

The interactions between expanding adipose tissue and the endothelium via adipokine secretions are shown in **Figure 6** [64].

7. Diabetes

Another factor that affects the process of neovascularization in skeletal muscle is diabetes. Diabetes is a risk factor for peripheral vascular diseases, and it is associated with impaired collateral vessel growth in skeletal muscle. Diabetes, in turn, has been demonstrated to impair skeletal muscle and cardiac angiogenesis, and the mechanisms underlying this have generated much interest recently. Both type 1 and type 2 diabetes have been shown to affect angiogenic growth factors and inhibitors in skeletal muscle [65, 66].

Several proangiogenic protein gene expressions decreased and increased those of antiangiogenic ones in in diabetic mouse skeletal muscle [66]. Hence, the imbalance between stimulators and inhibitors may lead to peripheral cardiovascular complications in diabetes [67, 68].

8. Angiogenic factors

To better understand the neovascularization of skeletal muscle, it is important to understand the current state of knowledge regarding different factors possessing angiogenic properties. The process of angiogenesis in skeletal muscle is controlled by a number of factors that are released in the tissues surrounding the small vessel involved, and it is thought to be controlled by net balance between pro-angiogenic (angiogenic) and anti-angiogenesis (angiostatic) factors. In skeletal muscle, the

balance of proangiogenic factors with antiangiogenic factors controls the extent of microvascular growth. For angiogenesis to occur, the balance of proangiogenic and antiangiogenic factors must favor the proangiogenic factors, and this has been termed the "angiogenic switch".

Therefore, a brief summary about the most well-known angiogenic (VEGF, FGF, and TGF) and angiostatic factors (endostatin, angiostatin, and thrombospondin-1) is presented here.

8.1 VEGF

Vascular endothelial growth factor (VEGF) is a 45 kDa secretable basic heparin-binding homodimeric glycoprotein. The human VEGF gene has been assigned to chromosome 6p21.3. Hypoxia is the main stimulus for VEGF production/expression. Observational studies support VEGF expression as an important factor for regulating skeletal muscle angiogenesis in both humans and animals [69, 70]. In patients with chronic disease conditions (e.g., chronic obstructive pulmonary disease, heart failure, and diabetes), as well as aging, locomotor skeletal muscle VEGF expression has also been reported to be lower, and these individuals often exhibit muscle weakness, reduced physical activity, and loss of skeletal muscle vascular density. A similar phenotype is found in sedentary (untrained) myocyte-specific VEGF gene ablated mice, which exhibit impaired exercise capacity and >50% loss of skeletal muscle microvessel density [71]. The human VEGF gene contains eight exons, seven introns, and a 14 kb coding region. VEGF has six different isoforms including VEGF165 (the predominant isoform), VEGF121, VEGF145, VEGF183, VEGF189, and VEGF 206 [72].

Binding of VEGF to the Flt-1 and KDR surface receptors activates their tyrosine kinase function resulting in enhanced endothelial cell proliferation, migration, vascular permeability, and protease activity [72, 73]. **Figure 7** shows several VEGF receptor signal transduction pathways that are known thus far.

8.2 FGFs

Currently, the family of FGFs consists of more than 20 members with 30.70% homology. FGFs are multifunctional proteins that bind to five cell membrane tyrosine kinase receptors (FGFR-1.5) and stimulate proliferation of a variety of cell types, including endothelial cells (ECs) and smooth muscle cells (SMCs). FGFs play a role in development, tissue regeneration, hematopoiesis, angiogenesis, and tumorigenesis. In vitro FGF-1, -2, -4, and -9 exert the highest mitogenic activity. Of these, FGF-1 and FGF-2 have previously been shown to induce therapeutic angiogenesis in vivo [75]. To the best of our knowledge, there are no published data about the potency of FGF-4 and FGF-9 in animal models [76].

8.3 Transforming growth factors (TGF-b) and platelet-derived growth factors (PDGF-BB)

Unlike VEGF and FGF, which are directly involved in the angiogenic process, TGF-b and PDGF-BB indirectly contribute to the angiogenic process. Mice lacking these two indicators die in utero due to defects in the process of vascular maturation. TGF and PDGF shear stress elements mediate upregulation of these factors in endothelial cells in response to increased shear stress in vitro.

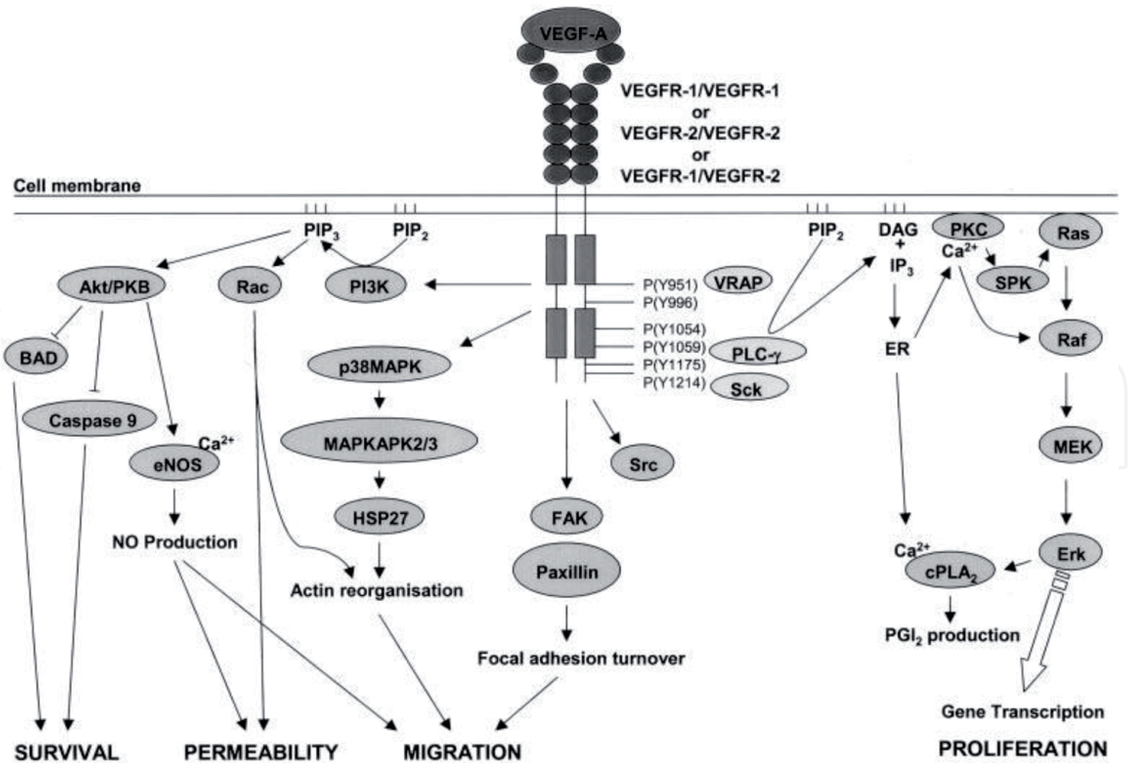

Figure 7.
VEGF receptor signal transduction. Several signal transduction pathways are activated by the binding of VEGF to its receptor, leading to increased proliferation, survival, permeability, and migration of cells [74].

PDGF also stimulates the proliferation of cultured smooth muscle cells and pericytes, both of which have been shown to express PDGF-b receptor [77].

TGF-b can control cell adhesion by regulating production of the extracellular matrix, stimulate or inhibit cell proliferation, protease inhibitors, and integrins, and induce cellular differentiation [78]. Much evidence points to an important role for TGF-b in the vasculature. It is clear that TGF-b recruits pericytes and smooth muscle cells in the arteriogenesis process [1].

8.4 Angiopoietin

During development and angiogenesis in adult tissue, there is a close relationship between a new group of factors, angiopoietins, and VEGF. The angiopoietins include angiopoietin 1 (Ang-1) and angiopoietin 2 (Ang-2). Similar to VEGF, angiopoietin receptors are located on the endothelial cells. For this reason, their function has been observed on endothelial cells. [79, 80]. Binding of Ang-1 to its receptors (Tie-2) maintains and stabilizes mature vessels by promoting interaction between the endothelial cells and surrounding cells [73]. In contrast, Ang-2 is thought to block the Tie-2 receptor and leads to vessel regression [73, 81]. It should to be noted that angiopoietins function depending on the VEGF present.

8.5 MMPs

Matrix metalloproteinases (MMPs) are a large family of protease enzymes and 26 members have been identified. Homeostasis of the extracellular matrix (ECM) in skeletal muscle dependent on MMP and TIMP balances [82]. The balance between angiogenic and anti-angiogenic factors interfere by MMPs via invoking angiogenic factors.

The ECM surrounds muscle fibers. ECM supports and protects muscle fiber and has a pivotal role in maintaining functional integrity of the fibers. Increased or decreased contractile activity of skeletal muscle promotes remodeling of the ECM. ECM degradation is a key step in the process of angiogenesis. Endothelial cells, stimulated by growth factors, produce MMPs that break down the cell membrane in physiological PH. Evidence is available that refers to the role of MMPs in the separation of smooth muscle cells from the extracellular matrix, and this allows the migration to cells [83].

Although several MMPs are found in skeletal muscle, mainly MMP-2 and MMP-9 play a more important role in skeletal muscle. MMP-2 and MMP-9 play an important role in skeletal muscle adaptation to changing contractile demands and to response to injury. MMP-2 and MMP-9 degrade type IV collagen and have important functions in homeostasis of the ECM during morphogenesis, proliferation, and cell apoptosis in a wide range of tissues. Expression of MMP-2 in skeletal muscle was increased following administration of chronic electrical stimulation, and expression of MMP-9 was increased after exposure to a chronic increase in blood flow [84].

8.6 Integrins

The communication between endothelial cells and the surrounding tissue (extracellular matrix: ECM) is affected by stretching via various mechanisms. Integrins are heterodimeric cell-surface receptors that link the cytoskeleton to the ECM; therefore, according to their status, integrins are involved in the vascularization process. One member of the integrin family, integrin αvβ3, is expressed on the surface of newly formed cells but is barely detectable in mature vessels. Differential expression of the alpha v family members may play a role in EC migration and apoptosis, though their role appears to be more complex than at first thought due to bidirectional signaling properties. Furthermore, interfering with integrin $\alpha_v\beta_3$ induces programmed cell death (apoptosis) in proliferating endothelial cells, which suggests its importance for the angiogenic process [80, 85, 86].

8.7 Follistatin-like 1

Follistatin-like 1 (Fstl1), also referred to as TSC36, is an extracellular glycoprotein that, despite limited homology, has been grouped into the follistatin family of proteins. Fstl1 is poorly understood with regard to its functional significance.

Studies indicated that Fstl1 is a secreted muscle protein or myokine that can function to promote endothelial cell function and stimulates revascularization in response to ischemic insult through its ability to activate Akt eNOS signaling [87].

8.8 Angiomotin

Angiomotin was recently identified as a new pro-angiogenic molecule. Angiomotin was detected at the surface of blood vessels of both healthy and pathological tissues such as placenta, retina, Kaposi's sarcoma, and breast tumors. Alternative splicing of angiomotin mRNA results in two protein isoforms of 80 and 130 kDa that exert very distinct roles during angiogenesis [88]. The p80 angiomotin isoform strongly stimulates *in vitro* and *in vivo* the migration of endothelial cells, a key event of the angiogenic process. Interestingly, angiostatin binding to angiomotin extracellular domain strongly inhibits such an effect. In contrast, p130 angiomotin isoform only exerts a very weak stimulatory effect on endothelial cell migration. The p130 protein was identified as tightly associated to cytoskeleton actin filaments

and highly involved in vessel stabilization and maturation [89]. Interestingly, skeletal muscles represent the most abundant tissue of the body and they express high levels of angiomotin. Moreover, microcirculation is a critical component of muscle function since capillaries provide myofibers with oxygen and nutriments, and remove carbon dioxide and metabolic waste. As myofibers respond to physiological or pathological conditions with a remarkable plasticity, it is crucial that the microcirculation remains well matched with the myofibers' needs in order to preserve muscle function. Depending on conditions, such muscle angio-adaptation can involve either angiogenesis or some vascular regression. Given its role not only during angiogenesis but also for vessel stabilization and maturation, angiomotin might thus represent an important factor in muscle angio-adaptation. To date, angiomotin expression in skeletal muscle has never been investigated in response to physiological or pathological conditionings [89].

8.9 EPH-B4/EPHRIN-B2

A unique class of receptor/ligand pair, Eph receptors and ephrin ligands, plays a prominent role in blood vessel development. Interestingly, not only does an ephrin expressed on the surface of one cell bind and activate its cognate Eph receptor on another cell, but through a reciprocal signaling mechanism the ephrin is also activated upon receptor engagement [90].

Ephrin-B2 as a member of the ephrin family is explicit on arterial endothelial cells, and its receptor eph-B4 is localized to venous endothelial cells.

Interaction of ephrin-B2 and its receptor has determined the primary capillary plexus after vasculogenesis [91]. The exact role of this interaction in the angiogenic process is not completely clear. But what has been approved is that establishment of contact and signaling between arterial and venous compartments mediated by ephrin-B2 and eph-4B is necessary for remodeling of the established primary capillary plexus [1].

9. Angiostatic factors

Vascularization can be suppressed at any of a number of key steps in this process by endothelial growth cycle disruption in which a quiescent vessel becomes an actively growing and invading endothelial tube.

In this regard, vasculogenesis can be blocked by different factors. Degradation of the extracellular matrix by activated endothelial cells can also be prevented, which suppresses sprouting and invasion of growing capillaries into their surroundings. Alternatively, endothelial cell proliferation can be inhibited by agents that block signaling within the cell and arrest its division cycle or by agents that prevent the maturation of nascent endothelial cells into functional tubes .Finally, endothelial cells can be forced to apoptose, which destroys the existing vessels and thereby impairs survival of vessel and metastasis through the vascular route.

In addition to the numerous factors that stimulate angiogenesis, both physiologically and pathologically, many substances including those mentioned above can inhibit blood vessel growth.

9.1 Angiostatin

Angiostatin is an internal fragment of plasminogen. Angiostatin was the first proteolytic fragment described with anti-angiogenic activity, derived from plasminogen via MMP degradation of plasmin.

Inhibition of NOS increased the expression of angiostatin and activities of MMP-2 and MMP-9 which generate it, suggesting that compromised NO production may lead to impaired angiogenesis during endothelial dysfunction. Whether there is any role in modulating flow-mediated angiogenesis is unknown. Four potential "receptors" for angiostatin have been identified: integrin $\alpha_v\beta_3$, ATP synthase, angiomotin, and the NG2 chondroitin sulfate proteoglycan (CSPG).

9.2 Endostatin

Endostatin is a 20-kDa carboxyl terminal proteolytic cleavage fragment of collagen type XVIII [92]. It is thought to be generated through a two-step process, as follows: a metal-dependent early cleavage of collagen type XVIII, followed by cleavage at an Ala-His site. It is not entirely clear which protease(s) is responsible for endostatin generation from collagen type XVIII in vivo, as multiple proteases can cleave recombinant fragments of human collagen type XVIII to generate endostatin-like fragments. In a study testing approximately 12 different proteases, elastase and cathepsin-L were the only two proteases found to efficiently cleave fragments of recombinant human collagen type XVIII, generating endostatin-like fragments. In support of a role for cathepsin-L in the generation of endostatin, cathepsin-L can proteolytically generate endostatin from its precursor in murine hemangioendothelioma cells propagated in vitro. Endostatin was originally reported to inhibit the proliferation of bovine capillary endothelial cells, but not the proliferation of cells of nonendothelial origin, and to also inhibit angiogenesis in the chick chorioallantoic membrane model [92] . Endostatin receptors that mediate the biological effects of endostatin are not yet clear. In this regard, research studies have shown that endostatin has the ability to bind to various cell surface molecules such as glypican, integrin α5β1, tropomyosin, and the VEGF receptor KDR/Flk-1 [93, 94].

9.3 Thrombospondin-1

Thrombospondin-1 (TSP-1) is a large (~450 kDa) multifunctional homotrimeric matrix glycoprotein whose action primarily serves to inhibit angiogenesis. Originally found to be stored and secreted in platelet α-granules, TSP-1 is now known to be produced by a wide variety of cells, including fibroblasts, keratinocytes, neutrophils, and macrophages and is believed to be a major secretory product of vascular smooth muscle and endothelial cells. The actions of TSP-1 include participation in platelet aggregation, inhibition of proteolytic enzymes, inhibition of endothelial cell proliferation, diminution of cell spreading, disruption of focal (cell-to-matrix) adhesions, and inhibition of angiogenesis *in vitro* and *in vivo*. However, the physiological relevance of TSP-1 in regulating skeletal muscle angiogenesis is not known. In these regard, Malek et al. showed that TSP-1 is an important endogenous negative regulator of angiogenesis that prevents excessive capillarization in the heart and skeletal muscles [95].

9.4 TIMPs

TIMPs inhibit MMP activities. Of the four TIMPs (TIMP-1, TIMP-2, TIMP-3, and TIMP-4) identified so far, TIMP not only has a direct effect on the growth and migration of endothelial cells, but also affects the extracellular matrix, which is an essential component of angiogenesis responses. The balance between stimulants and inhibitors of MMPs is a key step in the angiogenesis regulation. TIMP-1 and

TIMP-2 block the release of MMP-2 and MMP-9 zymogens, respectively. This factor reduces VEGF gene expression.

TIMP-1 is the most abundant type of TIMPs. TIMP-1 is a glycoprotein with a weight of 25.8 kDa and 184 amino acids, which has a variety of functions, such as growth factor activity, stimulation of morphological changes in cells, and prevention of angiogenesis. TIMP-1 with different gravities interacts with all known MMPs.

TIMP-2 is a nonglycolytic protein weighing 21 kDa and 196 amino acids, which prevents tumor growth. This protein mainly attaches to MMP-2. Of course, this factor, like TIMP-1, has the ability to connect to all MMPs.

TIMP-3 is a protein with a weight of 41 kDa and 188 amino acids, which causes cell death. This angiostatic factor specifically results in the deactivation of MMP-1, MMP-2, MMP3, and MMP-9. In this regard, TIMP-4 specifically connects to the MMP-2 and inhibits biological effects of MMP-2 [94].

9.5 Interferons

Interferons (INF-a, b, and g) are members of a family of secreted glycoproteins that were initially characterized for their antiviral effect. Interferons inhibit angiogenesis [96]. It is likely that IFN-a and IFN-b lead to downregulation of bFGF mRNA and protein levels [97] as well as its inhibitory effect on endothelial cell migration [1].

10. Conclusions

It is clear that a single paradigm cannot be used to encompass the unique patterns of capillary growth observed in response to various angiogenic stimuli. Over the past decade, novel markers of neovascularization in skeletal muscle have been identified, both at molecular and genetic levels, consequently leading our understanding of the molecular mechanisms involved in neovascularization of skeletal muscle to new heights. We have reviewed that the EC response during physiological angiogenesis within skeletal muscle is potentially sensitive to the hypoxia, shear stress, mechanical stimulus, and adenosine. A complex mix of humoral/metabolic and mechanical stimuli works coordinately within muscle to provide the cues that stimulate vascularization. The intricacies of these signaling pathways and levels of crosstalk between pathways remain to be elucidated. Although we still require delineation of signaling pathways evoked by individual angiogenic stimuli, a major goal for future research will be to determine how multiple stimuli are integrated within the capillary to determine a particular pattern of capillary growth. As mentioned, the process of vascularization in skeletal muscle depends on many factors such as angiogenic and angiostatic factors, but how their participation in the process of vascularization in the type of skeletal muscle fibers is not yet clear. Several key questions about the process of vascularization in skeletal muscle still remain to be addressed. For example: what is the relationship between intussusception, sprouting, angiogenic, and angiostatic factors and the type of skeletal muscle fibers? What is the relationship between angiogenesis factors secreted from muscle fibers and myosin heavy chains?

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References

[1] Papetti M, Herman IM. Mechanisms of normal and tumor-derived angiogenesis. American Journal of Physiology. Cell Physiology. 2002;**282**(5):C947-C970

[2] Shireman PK. The chemokine system in arteriogenesis and hind limb ischemia. Journal of Vascular Surgery. 2007;**45**(Suppl A):A48-A56

[3] Prior BM, Yang HT, Terjung RL. What makes vessels grow with exercise training? Journal of Applied Physiology. 2004;**97**(3):1119-1128

[4] Dufraine J, Funahashi Y, Kitajewski J. Notch signaling regulates tumor angiogenesis by diverse mechanisms. Oncogene. 2008;**27**(38):5132

[5] Egginton S. Physiological factors influencing capillary growth. Acta Physiologica (Oxford, England). 2011;**202**(3):225-239

[6] Egginton S. Invited review: Activity-induced angiogenesis. Pflügers Archiv. 2009;**457**(5):963-977

[7] Cai W, Schaper W. Mechanisms of arteriogenesis. Acta Biochimica et Biophysica Sinica Shanghai. 2008;**40**(8):681-692

[8] Helisch A et al. Impact of mouse strain differences in innate hindlimb collateral vasculature. Arteriosclerosis, Thrombosis, and Vascular Biology. 2006;**26**(3):520-526

[9] Hansen-Smith F et al. Growth of arterioles precedes that of capillaries in stretch-induced angiogenesis in skeletal muscle. Microvascular Research. 2001;**62**(1):1-14

[10] Kivela R et al. Effects of acute exercise, exercise training, and diabetes on the expression of lymphangiogenic growth factors and lymphatic vessels in skeletal muscle. American Journal of Physiology. Heart and Circulatory Physiology. 2007;**293**(4):H2573-H2579

[11] Coates G, O'Brodovich H, Goeree G. Hindlimb and lung lymph flows during prolonged exercise. Journal of Applied Physiology. 1993;**75**(2):633-638

[12] Havas E et al. Albumin clearance from human skeletal muscle during prolonged steady-state running. Experimental Physiology. 2000;**85**(6):863-868

[13] Fong GH. Regulation of angiogenesis by oxygen sensing mechanisms. Journal of Molecular Medicine. 2009;**87**(6):549-560

[14] Hudlicka O, Brown MD. Adaptation of skeletal muscle microvasculature to increased or decreased blood flow: Role of shear stress, nitric oxide and vascular endothelial growth factor. Journal of Vascular Research. 2009;**46**(5):504-512

[15] Haas TL. Molecular control of capillary growth in skeletal muscle. Canadian Journal of Applied Physiology. 2002;**27**(5):491-515

[16] Abumiya T et al. Shear stress induces expression of vascular endothelial growth factor receptor Flk-1/KDR through the CT-rich Sp1 binding site. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002;**22**(6):907-913

[17] Fredholm BB et al. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. Pharmacological Reviews. 2001;**53**(4):527-552

[18] Feoktistov I et al. Differential expression of adenosine receptors in human endothelial cells: Role of A2B receptors in angiogenic factor

regulation. Circulation Research. 2002;**90**(5):531-538

[19] Adair TH. Growth regulation of the vascular system: An emerging role for adenosine. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2005;**289**(2):R283-R296

[20] Ryzhov S et al. Role of adenosine receptors in the regulation of angiogenic factors and neovascularization in hypoxia. The Journal of Pharmacology and Experimental Therapeutics. 2007;**320**(2):565-572

[21] Bloor CM. Angiogenesis during exercise and training. Angiogenesis. 2005;**8**(3):263-271

[22] Huonker M et al. Size and blood flow of central and peripheral arteries in highly trained able-bodied and disabled athletes. Journal of Applied Physiology. 2003;**95**(2):685-691

[23] Magnusson G et al. Exercise capacity in heart failure patients: Relative importance of heart and skeletal muscle. Clinical Physiology. 1996;**16**(2):183-195

[24] Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation. 1990;**81**(2):518-527

[25] Drexler H et al. Alterations of skeletal muscle in chronic heart failure. Circulation. 1992;**85**(5):1751-1759

[26] Didion SP et al. Enhanced constrictor responses of skeletal muscle arterioles during chronic myocardial infarction. American Journal of Physiology - Heart and Circulatory Physiology. 1997;**273**(3):H1502-H1508

[27] Kindig CA et al. Impaired capillary hemodynamics in skeletal muscle of rats in chronic heart failure. Journal of Applied Physiology. 1999;**87**(2):652-660

[28] Schieffer B et al. Development and prevention of skeletal muscle structural alterations after experimental myocardial infarction. American Journal of Physiology - Heart and Circulatory Physiology. 1995;**269**(5):H1507-H1513

[29] Thomas DP, Hudlická O. Arteriolar reactivity and capillarization in chronically stimulated rat limb skeletal muscle post-MI. Journal of Applied Physiology. 1999;**87**(6):2259-2265

[30] Pogozelski AR et al. p38γ mitogen-activated protein kinase is a key regulator in skeletal muscle metabolic adaptation in mice. PLoS One. 2009;**4**(11):e7934

[31] Chinsomboon J et al. The transcriptional coactivator PGC-1alpha mediates exercise-induced angiogenesis in skeletal muscle. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(50):21401-21406

[32] Yan Z et al. Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle. Journal of Applied Physiology. 2011;**110**(1):264-274

[33] Zwetsloot KA et al. AMPK regulates basal skeletal muscle capillarization and VEGF expression, but is not necessary for the angiogenic response to exercise. The Journal of Physiology. 2008;**586**(Pt 24):6021-6035

[34] Gavin TP. Basal and exercise-induced regulation of skeletal muscle capillarization. Exercise and Sport Sciences Reviews. 2009;**37**(2):86-92

[35] Janacek J et al. 3D visualization and measurement of capillaries supplying metabolically different fiber types in the rat extensor digitorum longus muscle

during denervation and reinnervation. The Journal of Histochemistry and Cytochemistry. 2009;**57**(5):437-447

[36] Charifi N et al. Enhancement of microvessel tortuosity in the vastus lateralis muscle of old men in response to endurance training. The Journal of Physiology. 2004;**554**(Pt 2):559-569

[37] Badr I et al. Differences in local environment determine the site of physiological angiogenesis in rat skeletal muscle. Experimental Physiology. 2003;**88**(5):565-568

[38] Egginton S, Hudlicka O. Selective long-term electrical stimulation of fast glycolytic fibres increases capillary supply but not oxidative enzyme activity in rat skeletal muscles. Experimental Physiology. 2000;**85**(5):567-573

[39] Sullivan SM, Pittman RN. In vitro O2 uptake and histochemical fiber type of resting hamster muscles. Journal of Applied Physiology. 1984;**57**(1):246-253

[40] Ahmed SK et al. Is human skeletal muscle capillary supply modelled according to fibre size or fibre type? Experimental Physiology. 1997;**82**(1):231-234

[41] Cebasek V et al. Nerve injury affects the capillary supply in rat slow and fast muscles differently. Cell and Tissue Research. 2006;**323**(2):305-312

[42] Ranjbar K, Ardakanizade M, Nazem F. Endurance training induces fiber type-specific revascularization in hindlimb skeletal muscles of rats with chronic heart failure. Iranian journal of basic medical sciences. 2017;**20**(1):90

[43] Ranjbar K, Rahmani-Nia F, Shahabpour E. Aerobic training and l-arginine supplementation promotes rat heart and hindleg muscles arteriogenesis after myocardial infarction. Journal of Physiology and Biochemistry. 2016;**72**(3):393-404

[44] Panisello P et al. Capillary supply, fibre types and fibre morphometry in rat tibialis anterior and diaphragm muscles after intermittent exposure to hypobaric hypoxia. European Journal of Applied Physiology. 2008;**103**(2):203-213

[45] Murakami S et al. Comparison of capillary architecture between slow and fast muscles in rats using a confocal laser scanning microscope. Acta Medica Okayama. 2010;**64**(1):11-18

[46] Robbins JL et al. A sex-specific relationship between capillary density and anaerobic threshold. Journal of Applied Physiology. 2009;**106**(4):1181-1186

[47] Kyriakides ZS et al. Gender does not influence angiogenesis and arteriogenesis in a rabbit model of chronic hind limb ischemia. International Journal of Cardiology. 2003;**92**(1):83-91

[48] Keteyian SJ et al. Differential effects of exercise training in men and women with chronic heart failure. American Heart Journal. 2003;**145**(5):912-918

[49] Cui L et al. Arteriolar and venular capillary distribution in skeletal muscles of old rats. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2008;**63**(9):928-935

[50] Davidson YS et al. The effect of aging on skeletal muscle capillarization in a murine model. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 1999;**54**(10):B448-B451

[51] Coggan AR et al. Histochemical and enzymatic characteristics of skeletal muscle in master athletes. Journal of Applied Physiology. 1990;**68**(5):1896-1901

[52] Degens H et al. Capillary proliferation related to fibre types in

hypertrophied aging rat M. Plantaris. Advances in Experimental Medicine and Biology. 1994;**345**:669-676

[53] Parizkova J et al. Body composition, aerobic capacity, and density of muscle capillaries in young and old men. Journal of Applied Physiology. 1971;**31**(3):323-325

[54] Kano Y et al. Effects of aging on capillary number and luminal size in rat soleus and plantaris muscles. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2002;**57**(12):B422-B427

[55] Lyon MJ, Steer LM, Malmgren LT. Stereological estimates indicate that aging does not alter the capillary length density in the human posterior cricoarytenoid muscle. Journal of Applied Physiology. 2007;**103**(5):1815-1823

[56] Gavin TP et al. No difference in the skeletal muscle angiogenic response to aerobic exercise training between young and aged men. The Journal of Physiology. 2007;**585**(Pt 1):231-239

[57] Shimada T et al. Angiogenesis and vasculogenesis are impaired in the precocious-aging klotho mouse. Circulation. 2004;**110**(9):1148-1155

[58] Yu J et al. An engineered VEGF-activating zinc finger protein transcription factor improves blood flow and limb salvage in advanced-age mice. The FASEB Journal. 2006;**20**(3):479-481

[59] Shono N et al. Decreased skeletal muscle capillary density is related to higher serum levels of low-density lipoprotein cholesterol and apolipoprotein B in men. Metabolism. 1999;**48**(10):1267-1271

[60] Gudbjornsdottir S et al. Direct measurements of the permeability surface area for insulin and glucose in human skeletal muscle. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**(10):4559-4564

[61] Gavin TP et al. Lower capillary density but no difference in VEGF expression in obese vs. lean young skeletal muscle in humans. Journal of Applied Physiology. 2005;**98**(1):315-321

[62] Chou E et al. Decreased cardiac expression of vascular endothelial growth factor and its receptors in insulin-resistant and diabetic states: A possible explanation for impaired collateral formation in cardiac tissue. Circulation. 2002;**105**(3):373-379

[63] Toblli JE et al. Angiotensin-converting enzyme inhibition and angiogenesis in myocardium of obese Zucker rats. American Journal of Hypertension. 2004;**17**(2):172-180

[64] Rutkowski JM, Davis KE, Scherer PE. Mechanisms of obesity and related pathologies: The macro- and microcirculation of adipose tissue. The FEBS Journal. 2009;**276**(20):5738-5746

[65] Galasso G et al. Impaired angiogenesis in glutathione peroxidase-1-deficient mice is associated with endothelial progenitor cell dysfunction. Circulation Research. 2006;**98**(2):254-261

[66] Kivela R et al. Effects of experimental type 1 diabetes and exercise training on angiogenic gene expression and capillarization in skeletal muscle. The FASEB Journal. 2006;**20**(9):1570-1572

[67] Kivela R et al. Exercise-induced expression of angiogenic growth factors in skeletal muscle and in capillaries of healthy and diabetic mice. Cardiovascular Diabetology. 2008;**7**:13

[68] Boodhwani M et al. Functional, cellular, and molecular characterization of the angiogenic response to chronic

myocardial ischemia in diabetes. Circulation. 2007;**116**(11 Suppl):I31-I37

[69] Olfert IM et al. Myocyte vascular endothelial growth factor is required for exercise-induced skeletal muscle angiogenesis. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2010;**299**(4):R1059-R1067

[70] Prior BM et al. Exercise-induced vascular remodeling. Exercise and Sport Sciences Reviews. 2003;**31**(1):26-33

[71] Olfert IM et al. Muscle-specific VEGF deficiency greatly reduces exercise endurance in mice. The Journal of Physiology. 2009;**587**(Pt 8):1755-1767

[72] Lockwood CJ, Schatz F, Krikun G. Angiogenic factors and the endometrium following long term progestin only contraception. Histology and Histopathology. 2004;**19**(1):167-172

[73] Qazi Y, Maddula S, Ambati BK. Mediators of ocular angiogenesis. Journal of Genetics. 2009;**88**(4):495-515

[74] Hoeben A et al. Vascular endothelial growth factor and angiogenesis. Pharmacological Reviews. 2004;**56**(4):549-580

[75] Muhlhauser J et al. In vivo angiogenesis induced by recombinant adenovirus vectors coding either for secreted or nonsecreted forms of acidic fibroblast growth factor. Human Gene Therapy. 1995;**6**(11):1457-1465

[76] Rissanen TT et al. Fibroblast growth factor 4 induces vascular permeability, angiogenesis and arteriogenesis in a rabbit hindlimb ischemia model. The FASEB Journal. 2003;**17**(1):100-102

[77] Nicosia RF, Nicosia SV, Smith M. Vascular endothelial growth factor, platelet-derived growth factor, and insulin-like growth factor-1 promote rat aortic angiogenesis in vitro. The American Journal of Pathology. 1994;**145**(5):1023-1029

[78] Massague J. The transforming growth factor-beta family. Annual Review of Cell Biology. 1990;**6**:597-641

[79] Sato TN et al. Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessel formation. Nature. 1995;**376**(6535):70-74

[80] Gustafsson T, Kraus WE. Exercise-induced angiogenesis-related growth and transcription factors in skeletal muscle, and their modification in muscle pathology. Frontiers in Bioscience. 2001;**6**:D75-D89

[81] Holash J et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. Science. 1999;**284**(5422):1994-1998

[82] Carmeli E et al. Matrix metalloproteinases and skeletal muscle: A brief review. Muscle & Nerve. 2004;**29**(2):191-197

[83] John A, Tuszynski G. The role of matrix metalloproteinases in tumor angiogenesis and tumor metastasis. Pathology Oncology Research. 2001;**7**(1):14

[84] Carmeli E et al. High intensity exercise increases expression of matrix metalloproteinases in fast skeletal muscle fibres. Experimental Physiology. 2005;**90**(4):613-619

[85] Brooks PC, Clark RA, Cheresh DA. Requirement of vascular integrin alpha v beta 3 for angiogenesis. Science. 1994;**264**(5158):569-571

[86] Brooks PC et al. Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. Cell. 1994;**79**(7):1157-1164

[87] Ouchi N et al. Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric-oxide synthase-dependent mechanism. The Journal of Biological Chemistry. 2008;**283**(47):32802-32811

[88] Ernkvist M et al. Differential roles of p80- and p130-angiomotin in the switch between migration and stabilization of endothelial cells. Biochimica et Biophysica Acta. 2008;**1783**(3):429-437

[89] Roudier E et al. Angiomotin p80/p130 ratio: A new indicator of exercise-induced angiogenic activity in skeletal muscles from obese and non-obese rats? The Journal of Physiology. 2009;**587**(Pt 16):4105-4119

[90] Holland SJ et al. Bidirectional signalling through the EPH-family receptor Nuk and its transmembrane ligands. Nature. 1996;**383**(6602):722-725

[91] Wang HU, Chen ZF, Anderson DJ. Molecular distinction and angiogenic interaction between embryonic arteries and veins revealed by ephrin-B2 and its receptor Eph-B4. Cell. 1998;**93**(5):741-753

[92] O'Reilly MS et al. Endostatin: An endogenous inhibitor of angiogenesis and tumor growth. Cell. 1997;**88**(2):277-285

[93] Sudhakar A et al. Human tumstatin and human endostatin exhibit distinct antiangiogenic activities mediated by alpha v beta 3 and alpha 5 beta 1 integrins. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(8):4766-4771

[94] Rege TA, Fears CY, Gladson CL. Endogenous inhibitors of angiogenesis in malignant gliomas: Nature's antiangiogenic therapy. Neuro-Oncology. 2005;**7**(2):106-121

[95] Malek MH, Olfert IM. Global deletion of thrombospondin-1 increases cardiac and skeletal muscle capillarity and exercise capacity in mice. Experimental Physiology. 2009;**94**(6):749-760

[96] Ribatti D et al. Human recombinant interferon alpha-2a inhibits angiogenesis of chick area vasculosa in shell-less culture. International Journal of Microcirculation, Clinical and Experimental. 1996;**16**(4):165-169

[97] Singh RK et al. Interferons alpha and beta down-regulate the expression of basic fibroblast growth factor in human carcinomas. Proceedings of the National Academy of Sciences of the United States of America. 1995;**92**(10):4562-4566