



RESEARCH ARTICLE

Adipocyte-Endothelial Cell Crosstalk in Angiolipoma: Contribution of the Extracellular Galectin-1, -3 and -8 and their Binding Partners

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ABSTRACT

Angiolipomas are benign subcutaneous nodules composed of mature adipose tissue with thin-walled, dilated and tortuous small blood vessels, displaying intraluminal deposition of fibrin microthrombi formed from fibrinogen. The latter, considered not only as a diagnostic hallmark of angiolipoma, but also as a marker of vascular permeability. It is known that human adipose tissue (AT) growth, expansion, and maintenance is angiogenesis dependent and involves adipocytes, immune cells, fibroblasts, adipose stem cells and preadipocytes, all of them supported by an extracellular matrix. Interestingly, emerging evidence have emphasized that adipocytes maintain a bidirectional communication (crosstalk) with adipose endothelial cells (ECs) in healthy and pathological tissues and that this reciprocal and dynamic communication is crucial not only for the growth, expansion and maintenance of the AT, but also for the formation of new capillaries (angiogenesis) or microvasculature remodeling. However, the signals and mediators involved in this communication remain to be investigated.

Herein, we show that in angiolipoma GAL-1, -3 and -8 and some of their binding partners that includes proteoglycans such as perlecan, agrin, CD44 and endocan, as well as glycoproteins including TLR4, fibronectin, thrombospondin-1, integrin β_1 , PECAM-1, endoglin, VE-cadherin, and neuropilin-1, were immunolocalized around mature adipocytes that were in close proximity to small blood vessels, as well as in the ECs lining the lumen of these vessels.

We propose that in angiolipoma, GAL-1, -3 and -8 acting in concert with their binding partners form a supramolecular multivalent structure on the surface of mature adipocytes and ECs that might be facilitating the bidirectional communication (crosstalk) between adipocytes and ECs, contributing to the mature adipocytic expansion and the new vasculature formation (angiogenesis) or microvasculature remodeling.

Keywords: Angiolipoma, adipocyte, endothelial cell, crosstalk, galectins, Gal-glycan lattice

Introduction

Angiolipomas are benign subcutaneous nodules composed of mature adipose tissue with thin-walled, dilated and tortuous small blood vessels, displaying intraluminal deposition of fibrin microthrombi formed from fibrinogen. The latter, considered not only as a diagnostic hallmark of angiolipoma¹⁻⁷, but also as a marker of vascular permeability¹⁻⁹.

Equally well established is that human adipose tissue (AT) is comprised mainly of mature adipocytes with every adipocyte surrounded by one or more capillaries and that AT growth, expansion, and maintenance is angiogenesis dependent and involves adipocytes, immune cells, fibroblasts, adipose stem cells and pre-adipocytes. All of them supported by an extracellular matrix whose remodeling has been suggested is required for healthy AT expansion¹⁰⁻²⁸. Respect to AT growth, expansion and angiogenesis, *in vitro* studies revealed that AT explants in fibrin, collagen or matrigel, trigger blood vessel formation and that adipose ECs in turn promote preadipocyte differentiation, suggesting that the adipose ECs may be involved in the positive regulation of growth and maintenance of AT through their direct adhesion to mature adipocytes^{14,29-31}. Interestingly, emerging evidence have emphasized that adipocytes maintain a bidirectional communication (crosstalk) with adipose ECs in healthy and pathological tissues via endocrine and paracrine signals and that this reciprocal and dynamic communication is crucial not only for the growth, expansion and maintenance of the AT, but also for the formation of new capillaries (angiogenesis) or microvasculature remodeling^{17,23-26,28,32-35}. In this context, models of co-culture adipocyte-EC have been developed to study the crosstalk of mature adipocytes and ECs³⁶⁻³⁷. However, the signals and mediators involved in this communication remain to be investigated²⁸.

Of relevance, interplay between adipocyte and adipose EC during the formation of capillary structures involving the production of angiogenic factors by adipocytes, particularly vascular endothelial growth factor (VEGF), and the activation of their receptors tyrosine kinases (VEGFR1/VEGFR2) present on ECs, is well documented^{10,11,13,14,17,20,28,38,39}. Moreover, dynamic communication between adipocytes and ECs involving heparan sulfate proteoglycans (HSPGs) (e.g., perlecan, agrin, syndecan-1 (CD138) and chondroitin sulfate proteoglycans (CSPGs) (e.g., CD44, betaglycan) that surround both adipocytes and vascular structures has been recently reported^{18,24,35}. In addition, it has been suggested that paracrine activities exerted by free soluble proteoglycans as endocan, a small soluble dermatan sulfate proteoglycan (DSPG) (also known as endothelial cell specific molecule-1, ESM-1) expressed by adipocytes and activated capillary endothelial cells, are highly regulated by pro-angiogenic molecules such as VEGF and fibroblast growth factor (FGF)⁴⁰⁻⁴². Likewise, accumulating evidence have suggested that ECs^{7,43-48} and mature adipocytes^{49,50}, express Toll-like receptor (TLR) 2 and TLR4 on their surface and that both TLRs are activated by paracrine endogenous ligands that include fibrinogen, HSPGs, fibronectin (FN) and galectin-3, contributing to EC activation, formation of microvasculature, and inflammation^{44-49,51} as well as

adipocyte differentiation⁵²⁻⁵⁴. Thus, it is possible that both TLRs could be also participating in the crosstalk between adipocytes and ECs.

Another molecules that could be controlling this bidirectional communication in AT, are the soluble proteins family named galectins (GALs), particularly Galectin-1 (GAL-1), GAL-3, and GAL-8. GALs are a highly conserved family of 16 different small proteins identified in mammals. They are characterized by their ability to bind exposed β -galactosides motifs, particularly lactosamine (LacNAC) sequences in glycoconjugates and defined by the presence of one or two conserved Carbohydrate Recognition Domains (CRDs)⁵⁵⁻⁶¹. Individual GAL family members have been involved in many biological processes including cell-cell communication (crosstalk), cell-ECM interaction and angiogenesis⁶¹⁻⁷¹. Importantly, GALs function extracellularly and intracellularly⁵⁵⁻⁷¹. Extracellular GALs can appear arranged into non-covalent bound dimers and oligomeric forms able to bind and cross-link specific glycoconjugates containing N- and/or O-glycan residues or appear organized in supramolecular multivalent complexes known as galectin-glycan (GAL-glycan) lattices on the cell surface and in the extracellular milieu. The GAL-glycan lattices can mediate, through specific signaling pathways, cellular processes including cell-cell communication (crosstalk), cell matrix adhesion, proliferation, growth, differentiation, migration, and inflammation^{59-61,63,64,68,72-75}. Nevertheless, the current knowledge about how the aforementioned protein interactors would contribute to the bidirectional communication between adipocytes and AT endothelium, particularly in angiolipoma, is still limited. Thus, we believe that to understanding the interactions and contribution of these proteins to the crosstalk between adipocyte and EC in healthy and pathological tissues, including in angiolipoma, will be necessary to define which molecules could be participating.

In view of the above considerations, the purpose of this study was examine not only the presence and localization of GAL-1, -3, and -8 in angiolipoma tissue, but also consider the possibility that these GALs, acting in concert with some of their binding partners present on the adipocyte surface and on the abluminal and luminal sides of ECs, could be modulating the crosstalk between adipocyte and EC through the generation of lattices. Binding partners that contain N- and /or O-linked glycans in the extracellular domains and that include proteoglycans such as perlecan, agrin, endocan, and cluster of differentiation (CD) 44 (CD44), as well as glycoproteins such as TLR4, fibronectin (FN), thrombospondin-1 (TSP-1), integrin β 1, Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1, also known as CD31), endoglin (CD105), vascular endothelial cadherin (VE-cadherin), VEGFR2, and neuropilin-1 (NRP1).

Methods

Tissue samples

Eight biopsies were obtained from patients clinically and histopathologically (H&E staining) diagnosed with angiolipoma. Data regarding gender, age and site of lesion appear listed in Table 1. This study was approved

by the Ethics Committee of the University Hospital of Caracas and performed in line with the principles of the Declaration of Helsinki.

Table 1. Patients diagnosed with angiolipoma included in the study

| Patient | Gender | Age | Site of lesion |
|---------|--------|----------|-----------------|
| 1 | Female | 41 years | Thigh |
| 2 | Male | 62 years | Thigh |
| 3 | Female | 48 years | Arm |
| 4 | Male | 24 years | Arm |
| 5 | Male | 38 years | Wrist |
| 6 | Female | 48 years | Scapular region |
| 7 | Male | 28 years | Arm |
| 8 | Male | 56 years | Arm |

Indirect immunofluorescence staining of tissue sections

For each case, 4µm sections were cut from tissue blocks of biopsies that were previously fixed with formalin and embedded in paraffin. Sections were then set onto silanised glass slides. In order to remove the paraffin and to rehydrate the sections, they were first immersed in xylene, followed by a graded ethanol serie (from 100% to 70%), and rehydrated in distilled water and equilibrated in phosphate-buffered saline (PBS) for 10 min. Prior to incubation with the primary antibodies, sections were blocked for 1 hour in a humid chamber with phosphate-buffered saline (PBS) containing 3% BSA and 0.1% Tween 20, in order to prevent non-specific staining. Sections were then incubated with the primary antibodies diluted in PBS, 3% BSA, 0.1% Tween 20 (Table 2) for one hour at RT. Then, the sections were washed twice with PBS and incubated with anti-rabbit IgG Cruz Fluor 594 (Santa Cruz Biotechnology Inc., Dallas, TX, USA) diluted

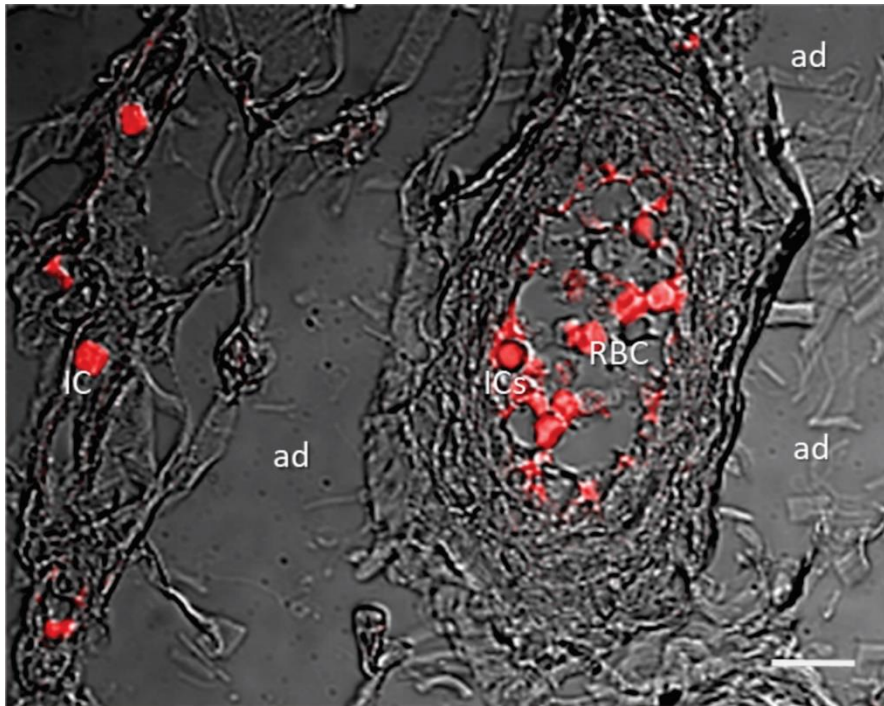
with PBS containing 3% BSA and 0.1% Tween20 for 30 min in a humid chamber in the dark. Finally, the sections were washed in PBS and mounted with glass coverslips using mounting medium containing 4',6-diamidino-2-phenylindole (DAPI) (Santa Cruz Biotechnology) for 15 min in the dark. All images were captured using a 1X81 Olympus inverted microscope with the Fluo View Confocal Laser Scanning configuration (CLSM) (Olympus America) equipped with software program FV10.ASW.

For autofluorescence, selected sections of 4µm dewaxed and without staining were examined with the CLSM. Autofluorescence was determined from the ratio between the emission fluorescence in the wavelength range between 603 and 646nm and the excitation light with a wavelength of between 491 and 592nm. To validate antibody binding specificity, some sections were incubated with only primary antibody or secondary antibody.

Table 2. Antibodies

| Primary antibody | Host | Producer |
|-------------------------|------------------|---|
| Agrin | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| CD44 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Endocan | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Endoglin (CD105) | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Fibronectin | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Galectin-1 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Galectin-3 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Galectin-8 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Integrin β ₁ | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Neuropilin-1 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| PECAM-1/CD31 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Perlecan | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| Thrombospondin-1 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| TLR4 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| VE-cadherin | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |
| VEGFR2 | Mouse monoclonal | Santa Cruz Biotechnology, Inc., Dallas, TX, USA |

Supplementary Figure



CLSM fluorescence image in the red wavelength, showing autofluorescence in red blood cells (RBCs) and ICs. ad, adipocyte. Scale bar: 45 μ m.

Results

Histopathological analysis of the angiolipoma tissue sections showed the mature adipose tissue (AT) with a variable number of dilated and tortuous small blood vessels containing fibrin microthrombi, red blood cells, and immune cells (Fig. 1a,b).

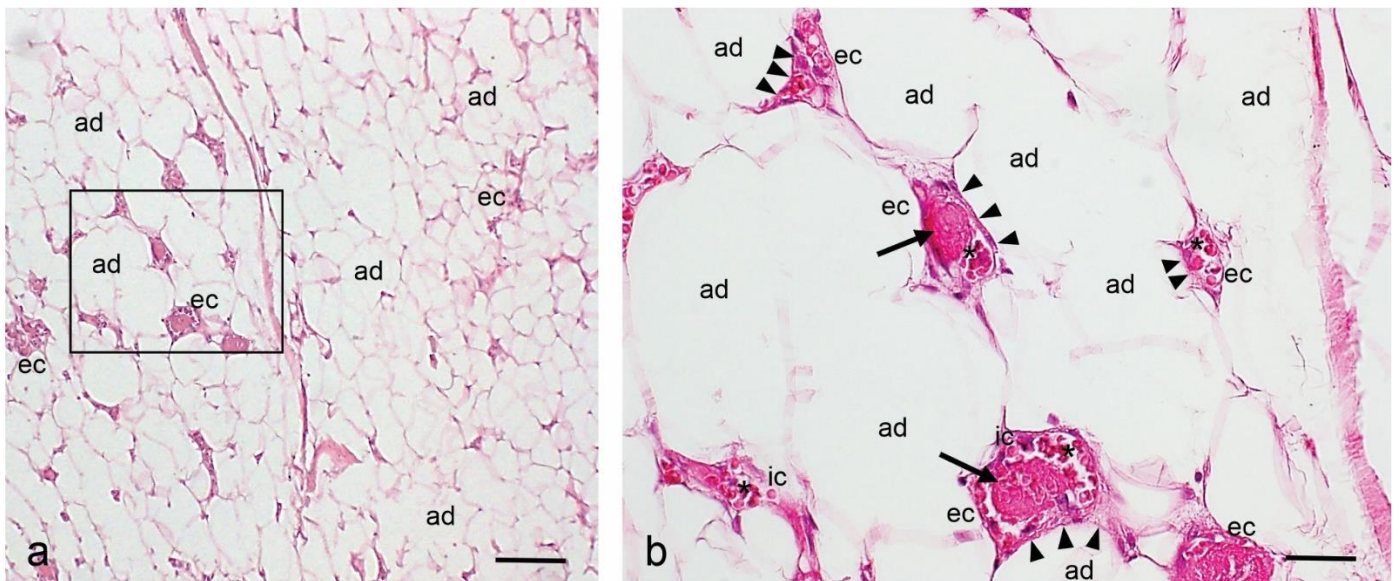


Fig. 1 a,b. Hematoxylin (H&E) staining from a biopsy of angiolipoma tissue located on thigh showing the mature adipocytes (ad) close to dilated and tortuous small blood vessels (arrowheads) containing fibrin microthrombi (arrows), red blood cells (asterisks), and immune cells (ic). ec, endothelial cells. Scale bars: 140 μ m; 35 μ m.

Immunolocalization of perlecan, agrin, endocan and CD44 in angiolipoma.

Because the proteoglycans perlecan, agrin, endocan and CD44 are heavily glycosylated proteins that comprise a core protein and one or more covalently attached linear and heterogeneous sulfated glycans (glycosaminoglycans, GAGs)⁷⁶⁻⁷⁹ and that they surround both adipocytes and vascular structures regulating the communication between adipocytes and ECs (crosstalk)³⁵, we examined the presence and localization of these proteoglycans in

the angiolipoma tissue sections selected. Immunofluorescence staining analyzed by confocal microscopy revealed that perlecan, agrin, endocan, and CD44 were present around the mature adipocytes that were in close proximity to small blood vessels (Fig. 2a-d). In addition, moderate immunoreactivity of these proteoglycans was also observed in the endothelial cells lining the lumen of these vessels, as well as in some immune cells (Fig. 2a-d).

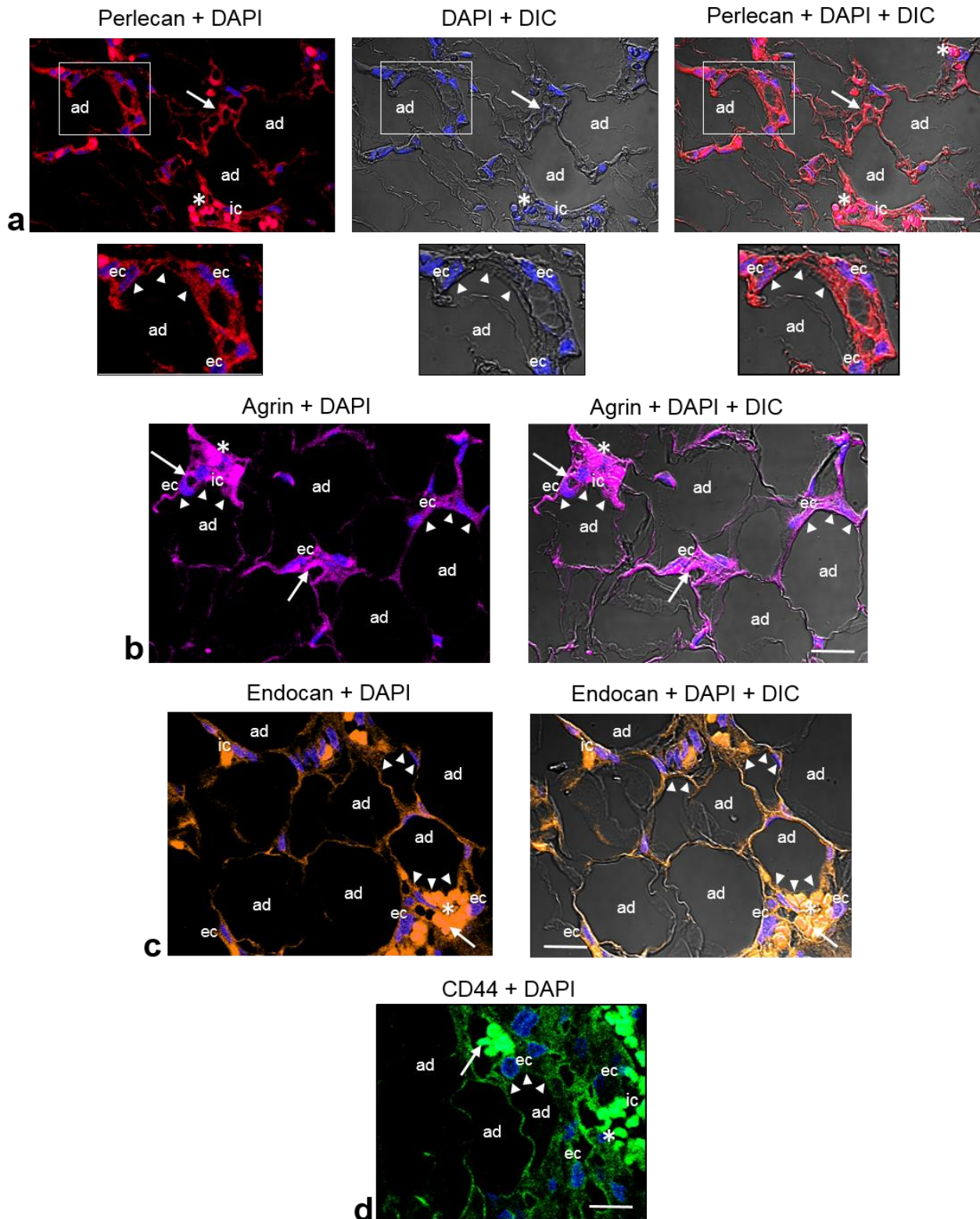


Fig. 2a-d. Representative CLSM fluorescence images of perlecan, agrin, and endocan in one biopsy of angioliipoma located on thigh, and CD44 in one biopsy of angioliipoma located on arm.

Perlecan (a), agrin (b), endocan (c), and CD44 (d) are immunolocalized around the mature adipocytes (ad) that are in close proximity to dilated and tortuous small blood vessels containing fibrin microthrombi (arrows), as well as in the ECs (ec) lining the vessel lumen and some immune cells (ic). Enlargements show the immunoreactivity for perlecan in the mature adipocyte (ad) in close proximity to the small blood vessels (arrowheads) and ECs (ec). Blue, nuclear DAPI staining; DIC, differential interference contrast image; red blood cells (asterisk). Scale bars: 70 μ m, 55 μ m (a); 45 μ m (b-d).

Immunolocalization of TLR4, fibronectin, and thrombospondin-1 in angioliipoma

We next examined the presence and localization of TLR4, fibronectin (FN), and thrombospondin-1 (TSP-1), glycoproteins that contain N-linked glycans^{46,80,81} and have been associated with angiogenesis and adipogenesis^{14,18}.

Examination of angioliipoma tissue sections selected revealed an intensive TLR4 immunoreactivity around the surface of mature adipocytes that were in close proximity to small blood vessels (Fig. 3a). For FN and TSP-1, less intense immunoreactivity was observed (b,c). Both were also observed around the mature adipocytes that were proximate to small blood vessels (Fig. 3b,c). Additional

immunostaining for TLR4, FN and TSP-1, was also evidenced in ECs lining the lumen of these vessels, as well as in some immune cells (Fig. 3a-c).

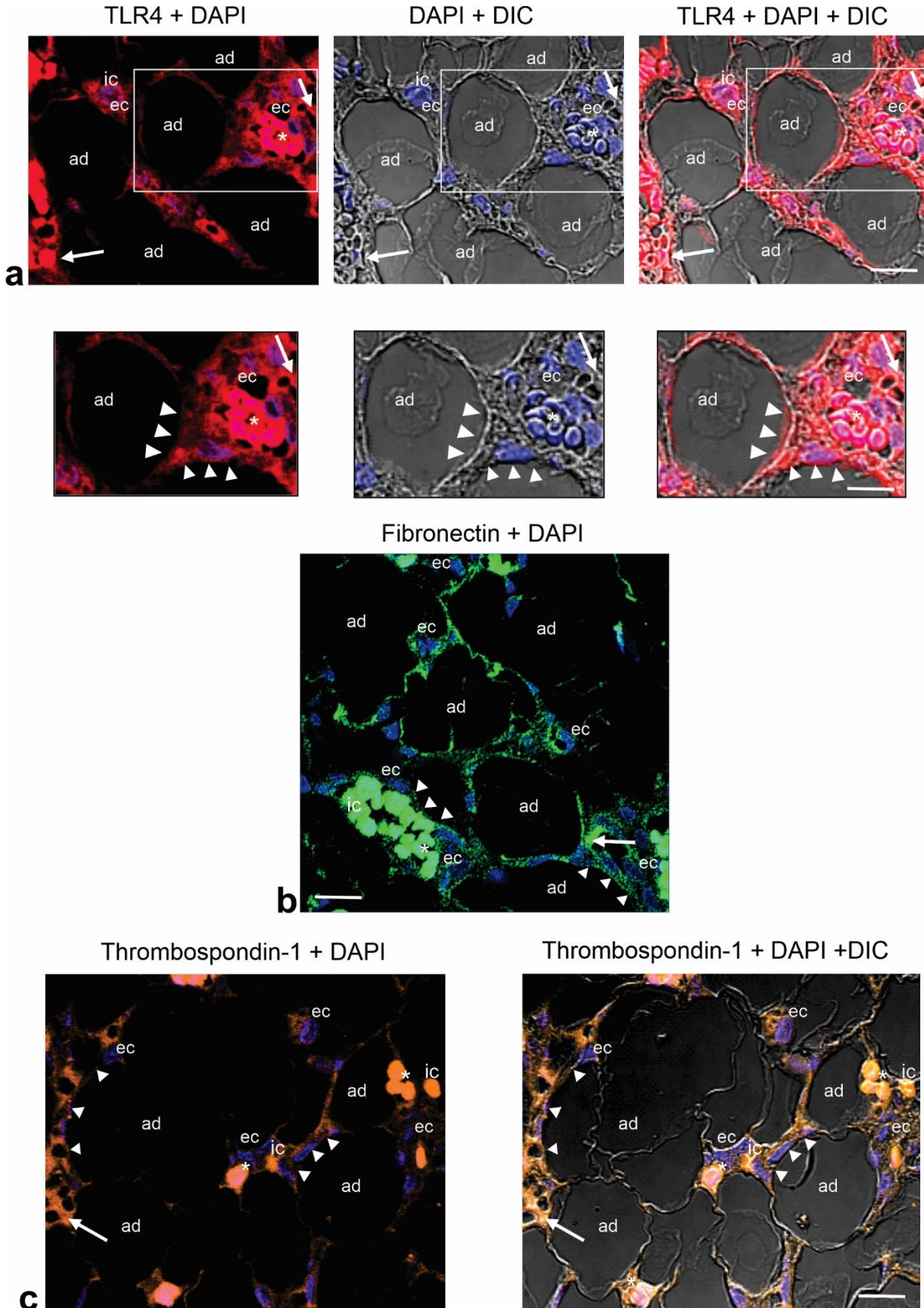


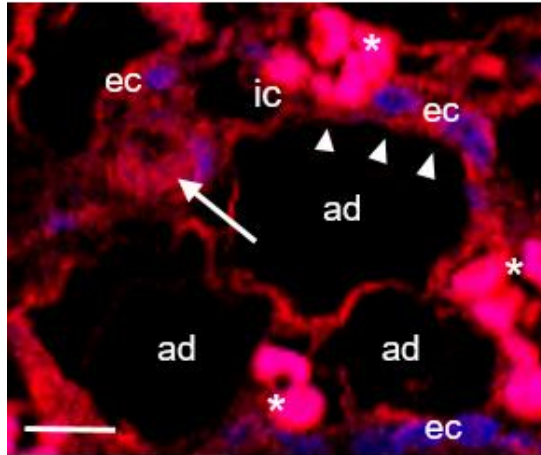
Fig. 3a-c. Representative CLSM fluorescence images of TLR4, FN, and TSP-1 in the angiolipoma located on thigh. TLR4 (a), FN (b) and TSP-1 (c) are immunolocalized around the mature adipocytes (ad) that are in close proximity to dilated and tortuous small blood vessels (arrowheads) containing fibrin microthrombi (arrows), as well as in the ECs (ec) lining the vessel lumen and some immune cells (ic). Enlargements show the immunoreactivity for TLR4 in the mature adipocyte (ad) in close proximity to the small blood vessels (arrowheads) and ECs (ec). Blue, nuclear DAPI staining; DIC, differential interference contrast image; red blood cells (asterisk). Scale bars: 45µm, 35µm (a); 35µm (b,c).

Immunolocalization of integrin β_1 in angiolipoma

Integrins contain N-linked glycans^{82,83} and are cell-surface adhesion molecules that bind to some specific extracellular matrix molecules including FN, TSP-1, and perlecan⁸¹⁻⁸⁵, and have been involved in adipogenesis^{86,87}, and in angiogenesis⁸⁸⁻⁹¹. We have therefore examined the presence and localization of

integrin β_1 subunit in the angiolipoma tissue sections selected. Immunolocalization with anti-integrin β_1 revealed that this subunit was localized around the mature adipocytes that were in close proximity to small blood vessels, as well as in the ECs lining the lumen of these vessels and some immune cells (Fig.4).

Integrin β_1 + DAPI



Integrin β_1 + DAPI + DIC

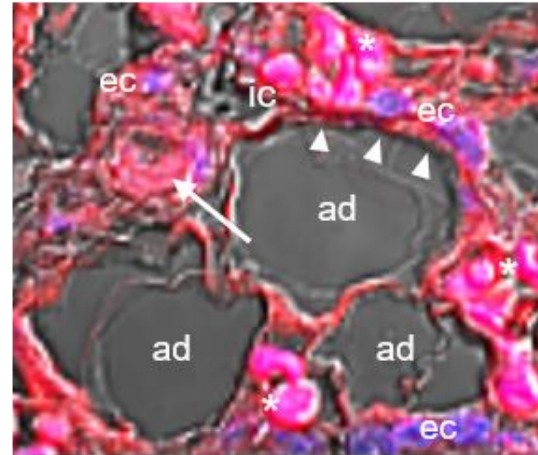


Fig.4. CLSM fluorescence image of integrin β_1 in the same biopsy (thigh).

Integrin β_1 subunit is immunolocalized around the mature adipocytes (ad) that are in close proximity to the small blood vessels (arrowheads) containing microthrombi (arrow), as well as in the luminal ECs (ec) and some immune cells (ic). Blue, nuclear DAPI staining; DIC, differential interference contrast image; red blood cells (asterisk). Scale bar: 35 μ m.

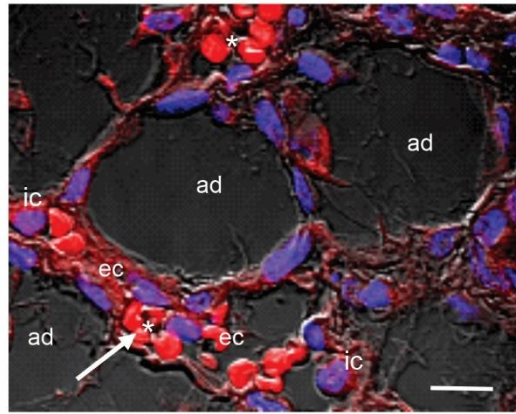
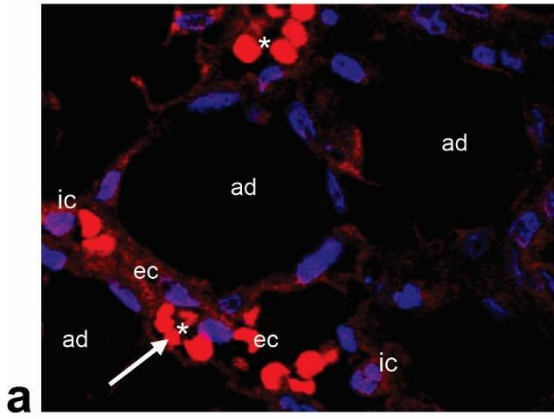
Immunostaining of PECAM-1/CD31, endoglin (CD105), VE-cadherin and VEGFR2 in angiolipoma

PECAM-1/CD31 is a transmembrane glycoprotein highly expressed on the surface of activated ECs that plays a critical role in the regulation of angiogenesis and vascular remodeling. It has an N-terminal ectodomain containing N-linked glycans residues, playing an important role in cell adhesion through homophilic interaction (that is, with PECAM-1) and heterophilic interactions with other glycoproteins including endoglin, VE-cadherin and

VEGFR2⁹²⁻⁹⁶, and proteoglycans such as CD44 and endocan⁹³⁻⁹⁵. Accordingly, we examined the presence and distribution of these glycoproteins in the small blood vessels of the angiolipoma tissue sections selected. Immunofluorescence showed that PECAM-1, endoglin, VE-cadherin and VEGFR2 were localized in the ECs of the tortuous and dilated small blood vessels (Fig. 5a-d). Likewise, moderate PECAM-1 and endoglin immunoreactivities were observed in some immune cells (Fig. 5a-d).

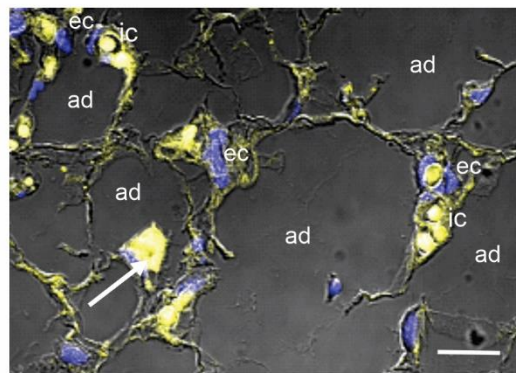
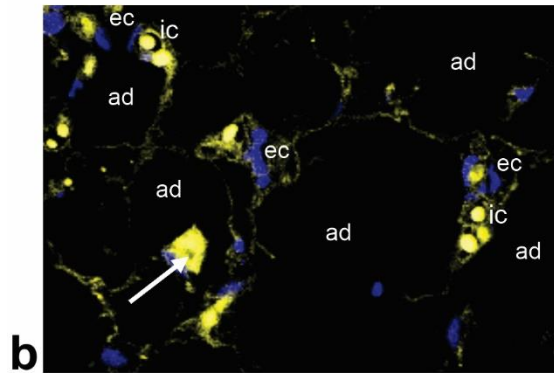
PECAM-1 + DAPI

PECAM-1 + DAPI + DIC



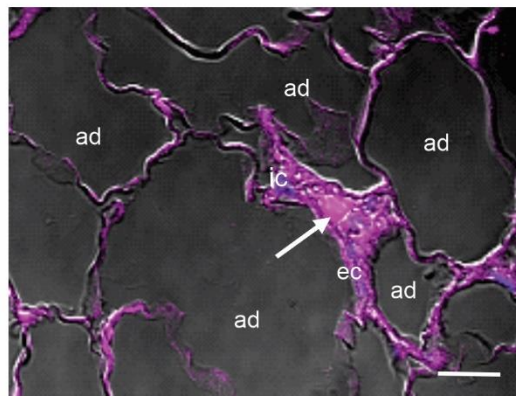
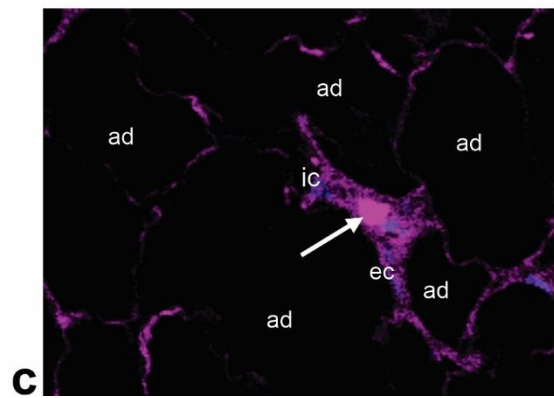
VE-cadherin + DAPI

VE-cadherin + DAPI + DIC



Endoglin + DAPI

Endoglin + DAPI + DIC



VEGFR2 + DAPI

VEGFR2 + DAPI + DIC

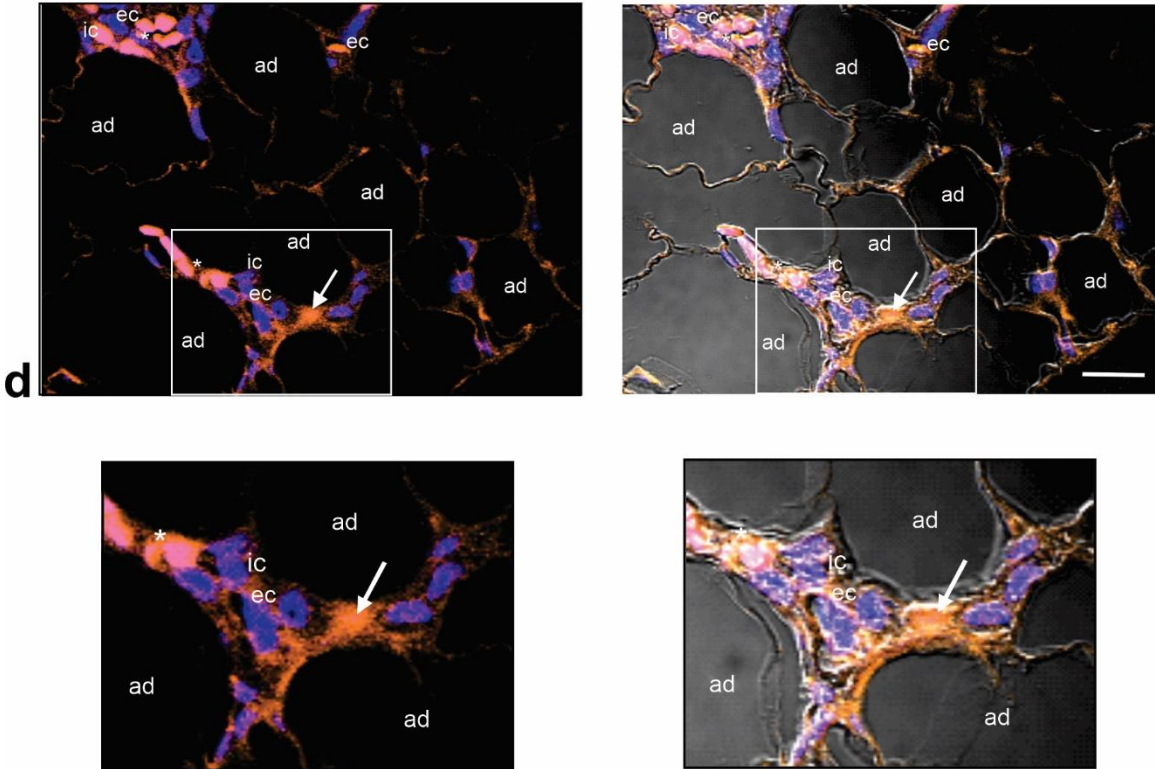


Fig. 5a-d. Immunostaining of PECAM-1 (CD31), VE-cadherin, endoglin, and VEGFR2 in the same biopsy (thigh). PECAM-1 (CD31) (a), VE-cadherin (b), endoglin (c) and VEGFR2 (d) are located in the ECs (ec) lining the lumen of the tortuous and dilated small blood vessels containing intraluminal microthrombi (arrows). Moderate PECAM-1 (CD31) and endoglin immunostaining is also observed in some immune cells (ic). Enlargement show the immunoreactivity for VEGFR2 in the ECs (ec). Blue, nuclear DAPI staining; DIC, differential interference contrast image; red blood cells (asterisk). Scale bar: 25 μ m (a); 35 μ m (b,c); 35 μ m, 20 μ m (d).

Overall, exacerbated immunopositivity in RBCs, ICs, and microthrombi provoked by autofluorescence at the red wavelength was observed in the selected sections (to see Methods section and supplementary File).

Immunolocalization of Neuropilin-1 in angiolipoma

Neuropilin-1 (NRP1) is a transmembrane glycoprotein expressed by several cell types including ECs⁹⁷⁻⁹⁹. It is

considered as a co-receptor for VEGFR2 facilitating VEGF binding and thus promoting the angiogenesis process^{97,99-101}. We have therefore examined the presence and distribution of this glycoprotein in the angiolipoma tissue sections selected. Immunofluorescence showed that NRP1 was localized in the ECs lining the lumen of tortuous and dilated small blood vessels (Fig. 6).

Neuropilin + DAPI

Neuropilin + DAPI + DIC

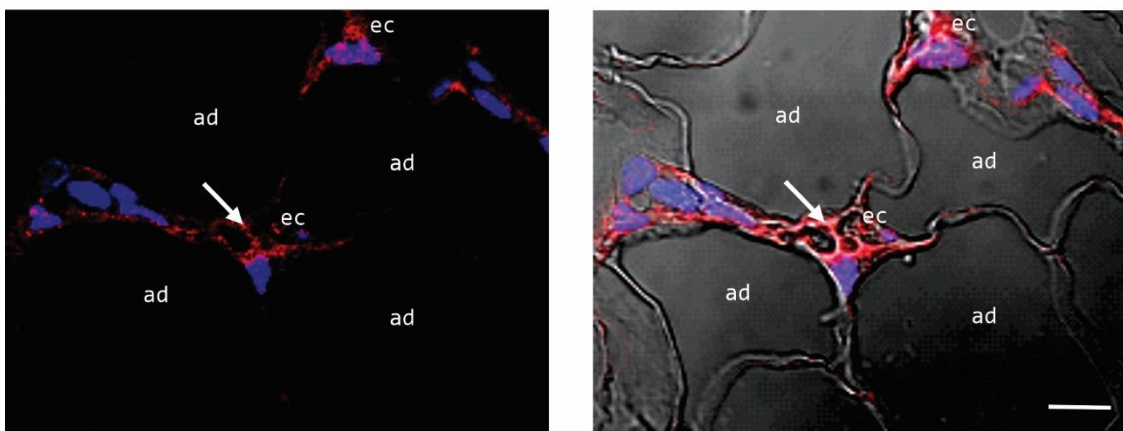


Fig. 6. Immunolocalization of neuropilin-1 (NRP-1) in the same biopsy (thigh).

NRP-1 is localized in the luminal ECs (ec) of the tortuous and dilated small blood vessels containing microthrombi (arrows). Blue, nuclear DAPI staining; DIC, differential interference contrast image; ad, adipocytes. Scale bar: 35 μ m.

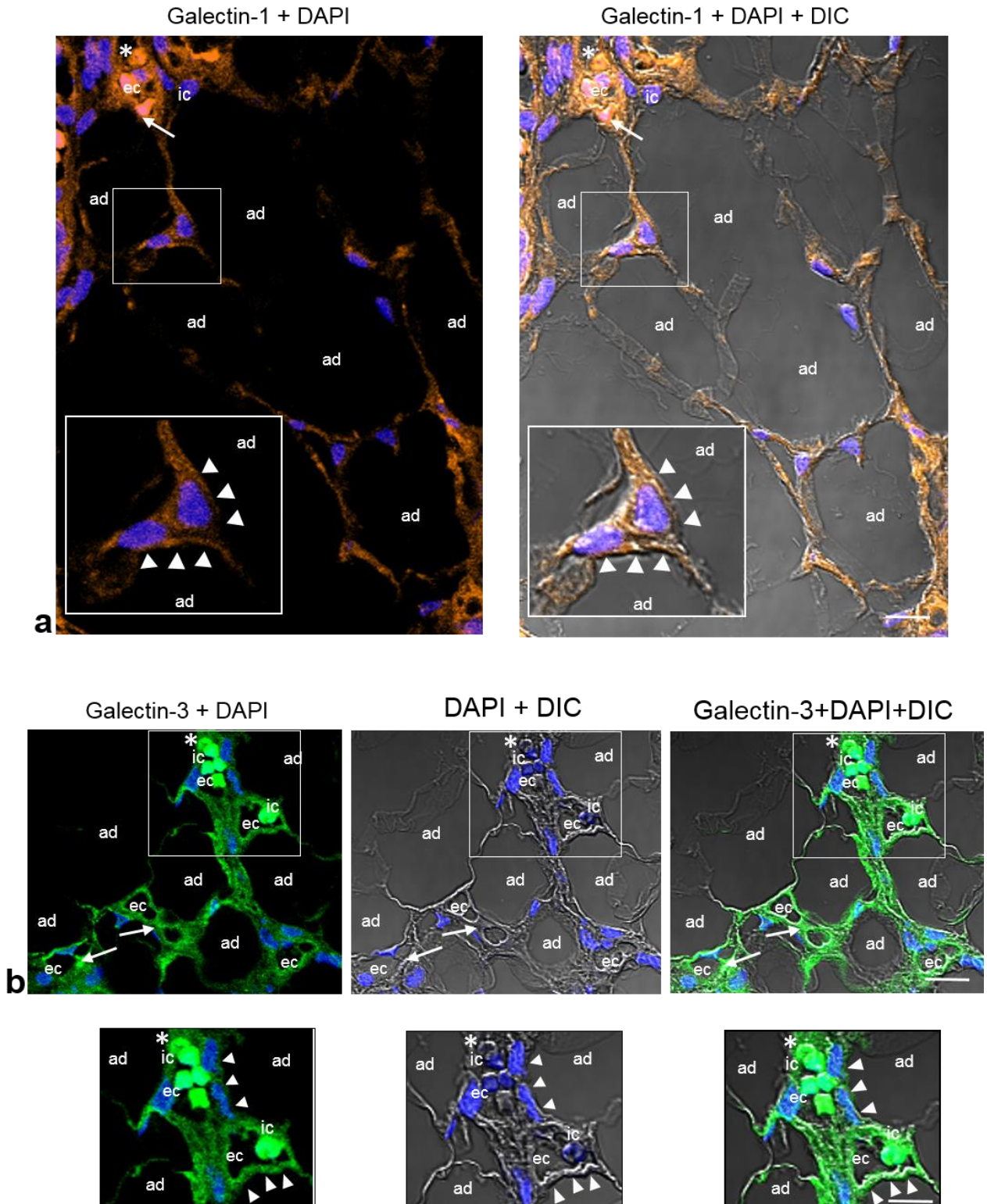
Immunostaining of GAL-1, GAL-3 and GAL-8 in angiolipoma

Given that GAL-1, GAL-3, and GAL-8 bind N- and/or O-linked glycan residues and that they not only promotes EC activation, angiogenesis and vascular remodeling^{62,65,66,69-71}, but also might play an important

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role in AT, modulating adipocyte proliferation and differentiation¹⁰²⁻¹⁰⁷, we next examined the localization and distribution of these galectins in the angiolipoma tissues selected. Immunofluorescence revealed an intensive immunoreactivity for GAL-1, -3 and -8 in the mature adipocytes that were in close proximity to

tortuous and dilated small blood vessels, as well in the ECs lining the lumen of these vessels (Fig. 7a-c). Additional immunostaining was also evidenced in some immune cells (Fig. 7a-c). No immunoreactivity was detected when the primary antibodies were omitted or replaced with PBS (not shown).



Galectin -8+DAPI

Galectin-8+DAPI+DIC

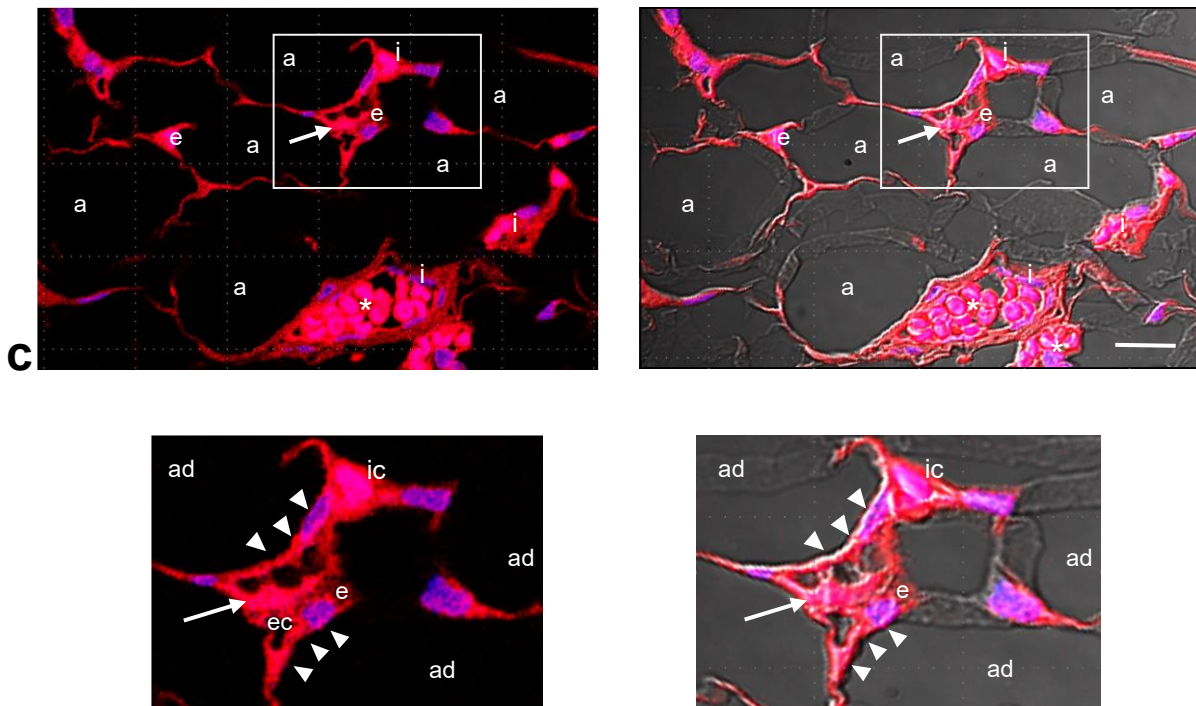


Fig. 7a-c. Representative CLSM fluorescence images of GAL-1, GAL-3, and GAL-8 in the same biopsy (thigh). GAL-1 (a), GAL-3 (b) and GAL-8 (c) are located around the mature adipocytes (ad) that are in close proximity to dilated and tortuous small blood vessels containing fibrin microthrombi (arrows), as well as in the ECs (ec) lining the vessel lumen and some immune cells (ic). Enlargements show the corresponding immunoreactivities in the mature adipocytes (ad) in close proximity to the small blood vessels (arrowheads), ECs (ec), and immune cells (ic). Blue, nuclear DAPI staining; DIC, differential interference contrast image; red blood cells (asterisk). Scale bars: 35 μ m, 20 μ m (a); 35 μ m, 25 μ m (b); 35 μ m, 20 μ m (c).

Discussion

In this study we showed that in angiolipoma tissues, the proteoglycans perlecan, agrin, CD44, and endocan were immunolocalized around mature adipocytes that were in close proximity to small blood vessels (arterioles, capillaries and venules), as well as in the ECs lining the lumen of these vessels and some immune cells. Remarkably, recent studies in AT have revealed the presence of HSPGs such as perlecan, agrin, CSPGs including CD44, and DSPG endocan, suggesting that these proteoglycans play an important role in the development and functioning of AT mediating the dynamic bidirectional communication (crosstalk) between adipocytes and microvascular ECs, promoting the uptake of lipids by adipocytes^{18,24,34,40-42}. Similarly, studies in the endothelial communication between adipose ECs and adjacent adipocytes through paracrine signals have suggested that the formation of capillary structures and AT expansion, involves the production of pro-angiogenic factors by adipocytes and ECs, particularly VEGF, and the activation of VEGFR1/VEGFR2 in ECs^{10,11,13,14,17,20,28,38,39}, as well as the participation of perlecan and endocan^{24,35}. Of note, overexpression of VEGF in AT leading to an increase in blood vessel number and size has been reported^{17,108,109}. With respect to the immunolocalization of TLR4, FN and TSP-1 around mature adipocytes and in the ECs of the small blood vessels, several studies have showed that ECs and adipocytes express TLR4 on their surface and that activation of this glycoprotein by some of their endogenous ligands such as fibrinogen, FN, HSPGs including perlecan, agrin, and GAL-3 contribute not only to the formation of

microvasculature and inflammation^{7,23,28,32,51}, but also to adipocyte differentiation (adipogenesis) and innate immunity^{49,52,54}. Therefore, it is plausible that perlecan, agrin, CD44, endocan, TLR4, and FN, could be mediating the adipocyte-EC crosstalk, contributing to the growth, expansion and maintenance of AT and the formation of small blood vessels in angiolipoma, which are cellular processes that could be accompanied by the production of VEGF and activation of VEGFR2.

Immunofluorescence also revealed that integrin β_1 -subunit was localized around the mature adipocytes that were in close proximity to small blood vessels, as well as in the ECs lining the lumen of these vessels and some immune cells. Consistent with this, studies on adipogenesis and integrins have proposed that regulation of the interaction between integrins, particularly integrin $\alpha_5\beta_1$ and $\alpha_v\beta_1$, and FN contribute to reorganization of the actin cytoskeleton and accomplishment of adipocyte differentiation (adipogenesis)^{86,87}. Similarly, studies in the AT vasculature have suggested that the interactions between adipocytes and ECs involving FN, collagens and integrin β_1 in the presence of VEGF, could be contributing to the angiogenesis expansion observed in AT^{20,24}. Thus, it is likely that integrin β_1 subunit could be mediating the adipocyte-EC crosstalk and contributing to the adipocyte growth, expansion and vascular remodeling in angiolipoma tissues.

Regarding the presence of PECAM-1, endoglin, VE-cadherin and VEGFR2 in the ECs lining the lumen of the tortuous and dilated small blood vessels, it is well known

that these molecules together with particular proteoglycans such as perlecan, CD44 and endocan and ECM components including the glycoproteins FN, TSP-1 and integrin β_1 , in combination with certain angiogenic factors produced by activated ECs including VEGF, are key for angiogenesis and vascular remodeling, as well as the regulation of vessel permeability^{13,14,20,34,110-114}. Of note, modulation of angiogenesis by perlecan through interaction of heparan sulfate side chains with growth factors especially VEGF, and several extracellular matrix components such as FN, TSP-1 and integrin β_1 , has been suggested^{81,112,113}. Moreover, interaction fibrinogen-EC involving endothelial integrins such as $\alpha_1\beta_5$ and $\alpha_v\beta_3$ and non-integrin receptors including PECAM-1, endoglin, VE-cadherin, as well as TLR4 and some of its endogenous ligands including fibrinogen/fibrin, facilitating the EC-EC and IC-EC interactions and, in turn, contributing to small blood vessels formation in angiolipoma, has recently been proposed⁷. Thus, the presence of PECAM-1, endoglin, VE-cadherin VEGFR2, together with activated TLR4 in the luminal ECs could be contributing to the AT angiogenesis and in turn, to the regulation of growth, expansion and maintenance of AT in angiolipoma.

In this study, immunostaining also revealed that NRP1 was present in the luminal ECs of the small blood vessels. Consistent with this, several lines of evidence indicate that NRP-1 act as co-receptor for VEGFR2 enabling the binding of VEGF and promoting the angiogenesis^{97,99-101}. Along these lines, overexpression of NRP1 resulting in the formation of excess capillaries, has been suggested⁹⁷. Additionally, NRP-1 multiprotein complexes formation with VEGFR2, endoglin, HSPGs, endocan, FN, integrin β_1 and GAL-1 on the EC surface regulating vascular permeability, has also been suggested^{97,115-118}. Moreover, recent studies have suggested the colocalization of NRP1 with VE-cadherin and HSPGs, transforming growth factor- β receptors (TGF β Rs) regulating adherens junction plasticity and inflammatory response^{101,115,118}. Therefore, we believe that interaction of NRP1 with the components of adherens junctions and endothelial surface including VE-cadherin, PECAM-1, VEGFR2, endoglin, HSPGs, integrin β_1 , and GAL-1, could be modulating angiogenesis in angiolipoma.

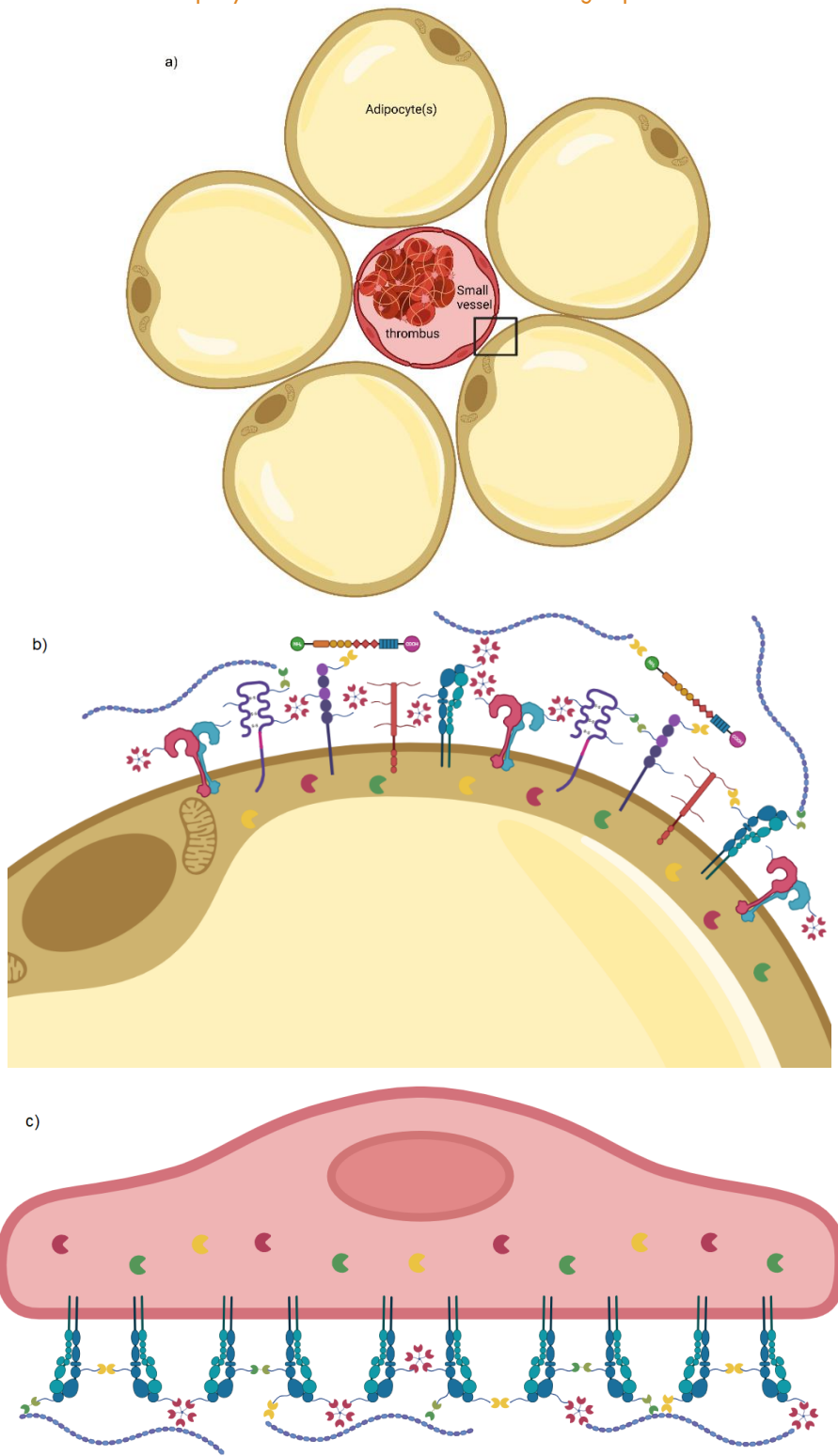
Interestingly, immunofluorescence also evidenced immunoreactivities for GAL-1, -3 and -8 in angiolipoma tissues on the surface of mature adipocytes that were in close proximity to tortuous and dilated small blood vessels, as well as in the ECs lining the lumen of these vessels. Noteworthy, studies *in vitro* and *in vivo* in AT have shown that GAL-1 and GAL-3 are expressed in adipocytes from both humans and animals, being considered as important for AT homeostasis and involved in the modulation of the differentiation and proliferation of adipocytes¹⁰²⁻¹⁰⁷. Similarly, studies on galectins have

suggested that secreted galectins, particularly GAL-1, -3 and -8, can remain in the vicinity of the cell either through binding and cross-linking to the N- and/or O-linked glycan residues of the glycoproteins or GAG side chains of the proteoglycans that are present on the cell surface or in the extracellular milieu^{56-59-67,72,119}. Some studies and others suggest that extracellular galectins can appear arranged into non-covalent bound dimers and oligomeric forms or appear organized in supramolecular multivalent complexes (GAL-glycan lattices) on the cell surface and in the extracellular milieu modulating, through specific signaling pathways, cellular processes including cell-cell communication (crosstalk), cell-matrix adhesion, proliferation, growth, differentiation, migration, and inflammation^{59-61,63,64,67-69,70,72-75,120-122}. It is therefore possible that in angiolipoma GAL-1, GAL-8 and GAL-3 can bind and cross-link the proteoglycans perlecan, agrin, CD44 and endocan and the glycoproteins FN, TSP-1, TLR4 and integrin β_1 generating GAL-glycan lattices on the surface of adipocytes and ECs.

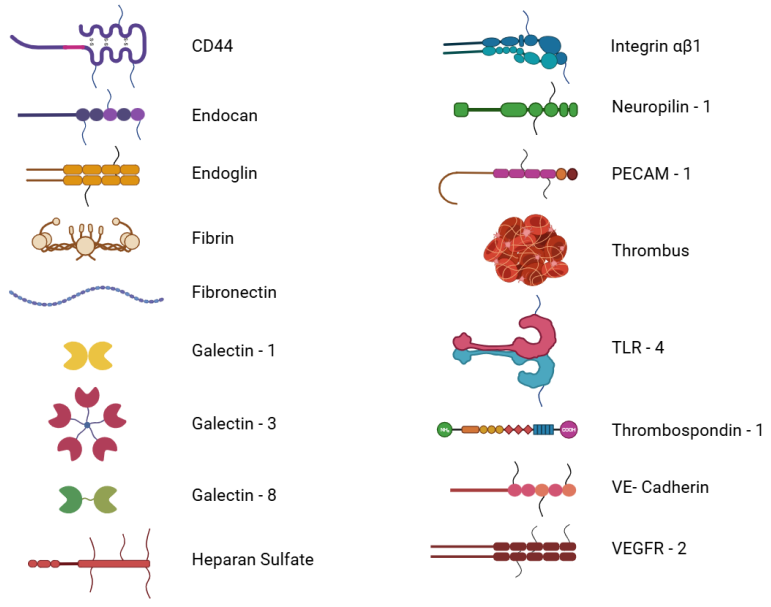
Regarding the presence of GAL-1, -3 and -8 in the ECs lining the lumen of small blood vessels, *in vitro* and *in vivo* studies have shown that EC activation upregulates the synthesis of GAL-1, -3 and -8, and that they are able to generate Gal-glycan lattices on the surface of ECs mediating the angiogenesis process through interactions with cell-surface glycoproteins that includes PECAM-1 (CD31), VE-cadherin, endoglin (CD105), integrin β_1 , and VEGFR2, proteoglycans such as perlecan, CD44 and endocan and certain glycoproteins that includes FN and TSP-1^{62,64,68,69-71,74,75,120-122}. Indeed, studies of GALs and angiogenesis indicate that GAL-1, -3 and -8 promote angiogenesis via activation of VEGFR2 signaling pathway^{87,92-95-97-99}, and that both GAL-3 and GAL-8 interact with integrin β_1 subunit regulating the adhesion to extracellular matrix components^{94,95}. Also, formation of GAL-1, NRP-1 and VEGFR2 complexes driving angiogenesis and inducing vascular permeability has been suggested^{61,98,115,121}. Other studies report that interaction of GAL-3 with PECAM-1 (CD31), endoglin (CD105) and CD44 stimulates EC migration and angiogenesis^{7,98,123}. Likewise, binding of GAL-3 to the β -galactoside residues present in the TLR2 and TLR4 ectodomains regulating innate and adaptive responses and promoting angiogenesis, has been proposed^{7,123}.

Ultimately, seems likely that in angiolipoma, GAL-1, -3 and -8 acting in concert with their binding partners, form a supramolecular structure on the surface of mature adipocytes and ECs that might be facilitating the bidirectional communication (crosstalk) between adipocytes and ECs and thus contributing to the mature adipocytic expansion and the new vasculature formation (angiogenesis) or microvasculature remodeling (Fig. 8).

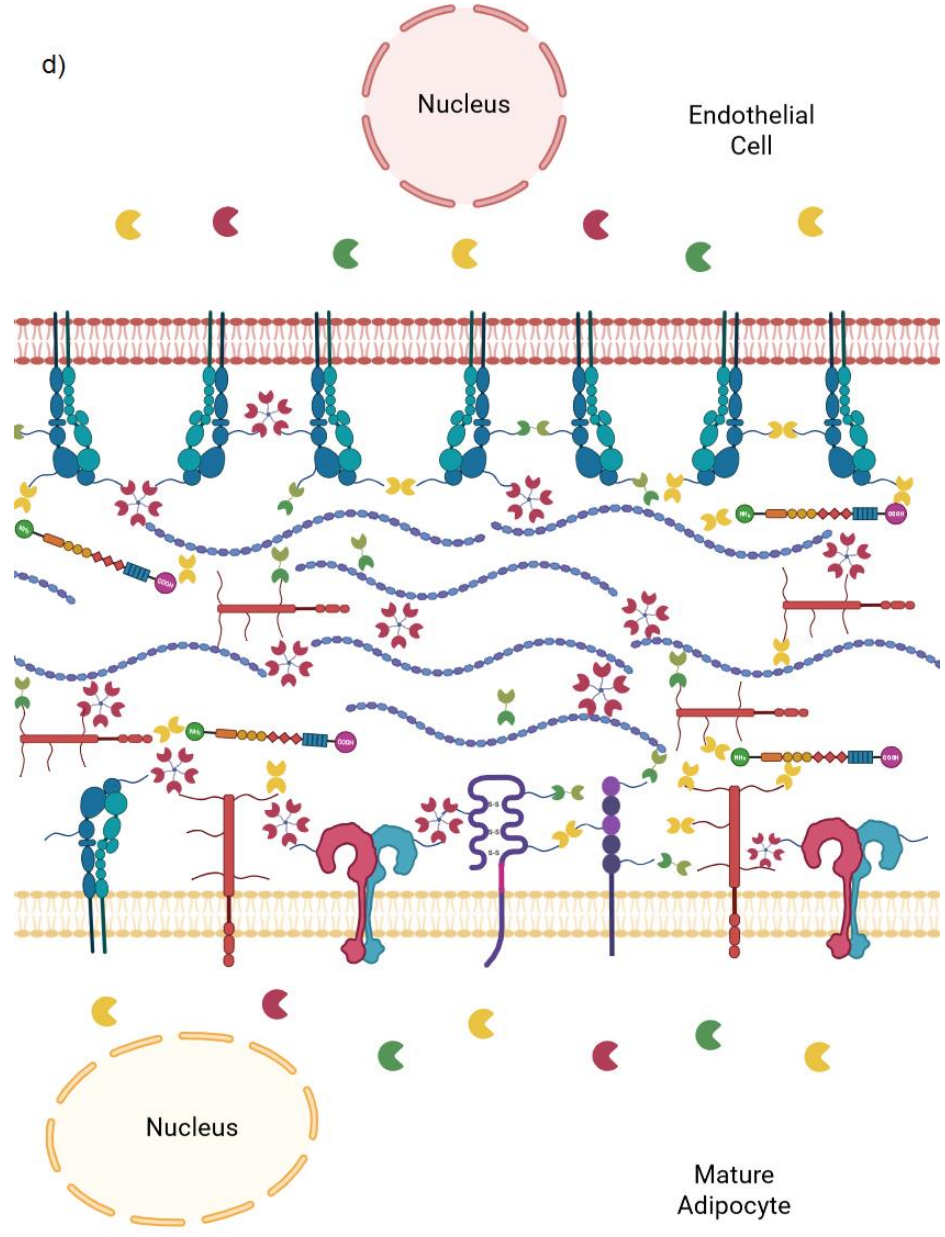
Adipocyte-Endothelial Cell Crosstalk in Angiolipoma



Adipocyte-Endothelial Cell Crosstalk in Angiolipoma



d)



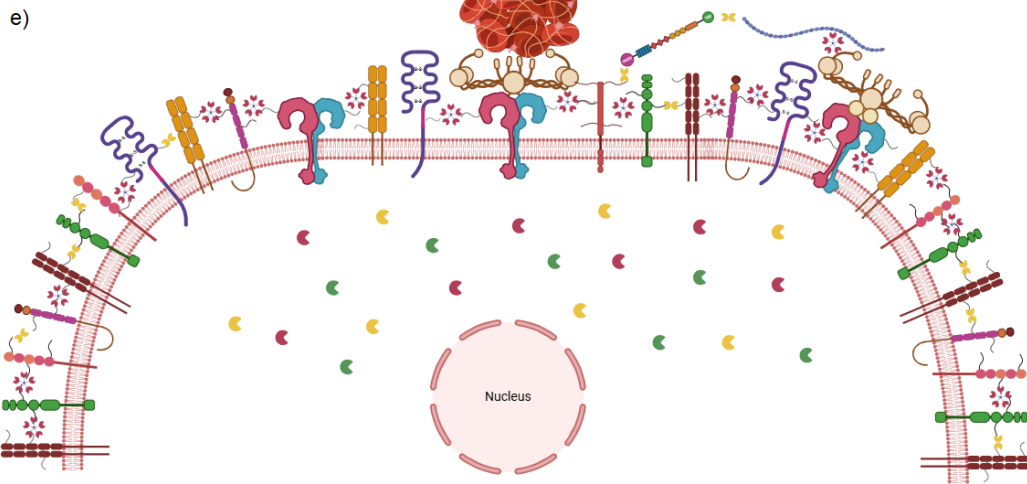


Fig. 8. Schematic representation of GAL-1, GAL-3, and GAL-8 forming a supramolecular multivalent structure (GAL-glycan lattice) through their binding partners.

a) Mature adipocytes and small blood vessel containing fibrin and microthrombus. b) GAL-glycan lattice on the mature adipocyte surface and extracellular milieu. c) GAL-glycan lattice on the abluminal side of endothelial cell. d) GAL-glycan lattice on the mature adipocyte surface, abluminal side of endothelial cell, and extracellular milieu. e) GAL-glycan lattice on the luminal side of endothelial cell.

Figures were drawn with BioRender (<https://www.biorender.com>)

Conclusions

We propose that in angiolipoma, GAL-1, -3 and -8 acting in concert with their binding partners form a supramolecular structure on the surface of mature adipocytes and ECs that might be facilitating the crosstalk between adipocytes and ECs, contributing to the mature adipocytic expansion and the new vasculature formation (angiogenesis) or microvasculature remodeling.

Statements and Declarations

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author contributions

E.A. analyzed the data and wrote the paper; A.D., H.R., A.S. and R.R. analyzed the data and constructed the images; A.D. constructs the scheme; J.P., A.U. and A.M.S. examined the biopsies. All authors read and approved the final manuscript.

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