Perspectives: MRI of angiogenesis ☆

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Abstract

Angiogenesis, the expansion of the vascular bed, is an important component in remodeling of tissues and organs. Such remodeling is essential for coping with substantial and sustained increase in the demands for supply of oxygen and nutrients and the timely removal of waste products. The vasculature, and its effectiveness in systemic delivery to all parts of the body, regulates the distribution of immune cells and the delivery of therapeutics as well as the dissemination of disease. Therefore, the vascular bed is possibly one of the key organs involved in homeostasis, in health and disease. The critical role of the vasculature in health, and the accessibility to noninvasive probing by MRI, renders MRI as a modality of choice for monitoring the vasculature and its adaption to challenges.

Keywords

Angiogenesis; MRI; Permeability; Vascular remodeling; Molecular imaging

1. Vascular remodeling and angiogenesis

The vascular system is required to cope with acute and sustained alterations in the requirements of organs to oxygen and nutrients. Such adaptation and responsiveness lies at the heart of maintaining cellular homeostasis in face of changing environment. Acute changes in demand can be accommodated by local changes in blood flow and perfusion, through vascular constriction or dilation, and changes in the permeability of the vessel wall. Beyond the impact on cellular metabolism, such changes can enhance immune response or block blood flow locally by activation of the coagulation cascade. The underlying unifying theme is that these responses locally alter blood flow due to localized challenge such as exercise [2]. This can be contrasted with systemic effects associated with changes in cardiac output or hormonal stimuli as observed for example for the effects of the hormone relaxin during pregnancy [3].

Prolonged local changes in tissue demand results in local structural change in the capillary bed, through angiogenesis, namely branching and sprouting of new vessels thus locally expanding the blood volume and vascular surface area. Typically, beyond the rise in capillary volume and surface area, local induction of angiogenesis often significantly alters the spatial organization of the capillary bed [4]. Structural changes can include increased

density of bifurcations and vessel branching, and often increase the tortuosity of vascular segments. While a mature well ordered vasculature is often fractal in nature, presenting similar structure across multiple scales, this is frequently not the case for sites of angiogenesis [5].

Structural changes in the vascular bed are reflected by corresponding changes in function. In particular, the functional parameters affected by angiogenesis include blood flow and perfusion, vasoreactivity in response to vasoactive challenges, and permeability of the vessel wall [6,7]. Such enhanced vascular leak can breach patency of vessels and break blood-tissue barriers (e.g. the bloodbrain barrier or the fetal-maternal barrier).

Structurefunction changes of the vessels are often accompanied by local changes in blood oxygenation and hemoglobin saturation. Less appreciated perhaps, is the impact of a change in vessel diameter on the local density of red blood cells, blood viscosity and hematocrit [8]. As red blood cells tend to flow in the fast moving center of the vessel while plasma flow is hindered by shear stress and wall interactions at the endothelial interface, changes in vessel diameter result in a change in the effective local hematocrit and viscosity of blood [9]. In the capillary environment, and particularly for sluggish blood flow in permeable dilated angiogenic vessels, blood cannot be regarded to be a classical viscous fluid. The local changes can result in induction of the coagulation cascade, in deposition of intravascular plaques and in activation of blood born and tissue resident immune cells.

Multiple types of cells take part in execution of the angiogenic program [10,11]. The best studied participants are vascular endothelial cells which line the vessels in nearly all organs and provide the smooth continuous inner lumen through which blood can flow. During angiogenesis, endothelial cells from the vessel wall must divide, migrate and adhere to form new vessels, without disrupting the flow of blood during this process. This is a remarkable feat for cells that typically remain dormant and survive with no cell division or cell death for many years. In special cases cells that are not endothelial in origin, adopt an endothelial phenotype and line blood vessels [12]. A physiological example for vascular mimicry is that of fetal trophoblast cells, which invade the maternal uterine spiral arteries and replace maternal endothelial cells, so as to control the flow of maternal blood into the maternal circulation of the placenta [13].

Plasticity of the vascular bed is enabled by the dissociation of perivascular contractile pericytes and vascular smooth muscle cells. These are the cells that constrict or dilate vessels in response to vasoactive challenges [14]. Fibroblasts and Immune cells of the stroma support angiogenesis by altering the production of growth factors, enzymes and structure of the extracellular matrix, so as to shift its property from quiescent, mature, anti angiogenic into a reactive proangiogenic provisional matrix. A significant role in activation of the extracellular matrix can be attributed to the elevated vascular permeability resulting in extravasation of plasma proteins and activation of coagulation to deposit a fibrin clot [15]. Multiple MRI tools were developed for detection of angiogenesis induced vascular permeability, vascular expansion and vascular maturation [16–18].

2. Vascular endothelial growth factor (VEGF)

It is remarkable that a single growth factor is required and sufficient for orchestrating vascular remodeling in multiple developmental, physiological and pathological processes, including the entire cascade from induction of vascular permeability, to endothelial cell proliferation, migration and tube formation. These activities are delivered by the master regulator of angiogenesis, vascular endothelial growth factor A (VEGFA; originally isolated as vascular permeability factor VPF) [19–21]. With delivery of oxygen being the most critical role of the vasculature, it makes sense the angiogenesis will be regulated by oxygen. Indeed, the role of oxygen as a mediator of vascular stability, whereby local hypoxia serves as a local signal for vascular expansion, was raised as hypothesis before the molecular mechanism of angiogenesis was identified [22].

With the discovery of VEGF as the primary mediator of angiogenesis, it's regulation by hypoxia was discovered in both pathogenic as well as developmental and physiological angiogenesis [23,24]. The molecular machinery includes intracellular mechanism for oxygen sensing and its transmission for modulating the expression of VEGF. Hypoxia inducible factor 1 (HIF1) was implicated in mediating the cellular response to oxygen deficiency. This link between hypoxia, HIF, VEGF and angiogenesis was demonstrated in numerous systems and revealed by MRI analysis of vascular remodeling [25–28].

3. Receptors and cell surface markers of angiogenesis

VEGF activates angiogenesis by binding tyrosine kinase VEGF receptors found on the surface of endothelial cells [29]. The primary receptor active in induction of angiogenesis is VEGFR2. Among the other family members, VEGFR1 has higher affinity to VEGF and can thus act as an anti angiogenic VEGF trap, particularly when expressed as a soluble secreted protein (soluble Flt). Another family of vascular cell surface receptors is the Tie receptors, which respond to angiopoietins, and affect the interaction of endothelial cells with perivascular pericytes [30]. Ang1 promotes vascular survival and proliferation while Ang 2 acts as an antagonist, inducing vascular pruning [31]. Transgenic mice showed consistency of the roles of VEGFR2/Flk1 and Tie2/Tek during early angiogenesis and during subsequent vascular marturation respectively [31–33].

Cell surface receptors were evaluated as targets for therapy and for molecular imaging. Suppression of VEGF signaling either by ligation of the ligand or by inhibition of the receptor is the primary approach for anti angiogenic therapy. Such treatments showed significant efficacy in reducing blindness due to macular degeneration [34], however their efficacy in blocking cancer progression was considerably lower than originally hoped for [35]. As targets for molecular imaging by MRI, the primary cell surface marker that was studied is $\alpha V\beta 3$, an endothelial integrin, which is induced during angiogenesis but is also ubiquitously expressed by other cells [36]. Utilizing nanoparticle based contrast media, including iron oxide particles or Gd decorated liposomes, regions of angiogenesis could be highlighted by the enhanced retention of vasculature targeted imaging contrast media [36–41].

4. ECM building blocks and enzymes

The extracellular matrix (ECM) maintains the quiescent vasculature by providing potent anti angiogenic cues. Induction of angiogenesis is accompanied and regulated by extensive changes of the ECM to form a reactive stroma, which is part of the granulation tissue of the wound repair machinery. Tumors hijack this wound healing machinery, as elegantly described in the hypothesis raised by Herald Dvorak that tumors can be viewed as wounds that do not heal [42]. The molecular constituents of the reactive angiogenic stroma include the replacement of collagen by fibrin; breakdown of collagen by MMPs and breakdown of Heparan and hyaluronan by heparanase and hyaluronidase. These enzymatic reactions release adherent growth factors from the ECM thereby further enhancing the angiogenic response [43]. Smart sensors for detection of ECM remodeling in angiogenesis provide an attractive tool for detection of the role of the activated matrix [17].

5. Mammalian reproduction

The ovary undergoes cycles of follicular development, expansion, ovulation and formation of a corpus luteum. This ovarian cycle includes extensive remodeling of the vascular bed. The cumulus cells surrounding the oocyte in the core of the developing follicle are exposed to hypoxia with follicular expansion, consistent with induction of VEGF expression [16]. The corpus lutetium development includes further substantial angiogenesis. Vascular leak in the ovary is high, and can be detected by DCE MRI particularly with the use of macromolecular contrast media [16,44–47].

One of the key processes for survival of mammalian species is embryo implantation and pregnancy. Survival of the nonsyngeneic embryo in the uterus of immune competent mother is one of the major mysteries of immune tolerance. Clearly the maternal vascular adaptation to pregnancy must include the requirement for effective mechanism for delivery of nutrients and oxygen to the growing fetus, while maintaining strict isolation between the maternal circulation and that of the fetus.

Although not observed yet for human, enhanced vascular leak in implantation sites is readily observable by MRI in pregnant mice as early as day 4.5, namely a few hours after adhesion [48]. Furthermore, MRI can be used for detection of the impact of specific challenge including genetic alteration or ablation of immune cells on implantation [49,50]. Further in pregnancy, the placenta effectively separates between the fetal and maternal circulation. Contrast enhanced MRI shows the barrier functions towards macromolecular contrast media, which low MW contrast media can be transported across to the fetal circulation [51–54]. Remarkably, the maternal blood flows through the placenta in spaces lined by embryo derived trophoblast cells, which mimic and replace the maternal endothelial cells.

6. Cancer

The tumor angiogenic switch hypothesis was raised by Folkman et al. 45 years ago [55,56]. Briefly this hypothesis set the foundation for the field of cancer angiogenesis, by suggesting that cancer cells can progress in the absence of new blood vessels only to form microscopic, millimeter size dormant nodules. Induction of angiogenesis requires a new additional genetic

change so as to induce the production of postulated TAF, tumor angiogenic factor, which will induce sprouting of capillaries, thus enabling the tumors to progress [56]. The major support for this theory is the prevalence of avascular microscopic tumor nodules which can be found in people who died from non-cancer causes [57], suggesting that malignant transformation is necessary but is not sufficient for clinical progression of cancer and that angiogenesis may be the dominant prognostic factor.

The prevalence of dormant tumors, which lie within the detection level provided by liquid biopsies (namely omics measurements of blood samples) or detectable by imaging, raise the problem of over diagnosis which can accompany early detection, and highlights the need for improved prognostic differential markers that can be used for surveillance as alternative to intervention. The induction of angiogenesis was suggested to provide such a marker which can be easily tracked by MRI.

When the tumors progress, angiogenesis is required to sustain the growing needs of the tumor. However, the elevated permeability and the irregular vascular patterning, with high tortuosity and low vasoreactivity result in sluggish blood flow and elevated interstitial fluid pressure [58–60]. Thus, tumors often exhibit both hypoxia and high angiogenesis and vessel permeability, both of which are associated with poor patient outcome [55,61]. Inhibition of angiogenesis results in vascular trimming and suppression of vascular leak, resulting in "normalization" of the vessels and enhanced response to radiation and chemotherapy [62]. This normalization of the vasculature could be detected in patients by MRI [63–65]

7. MRI of angiogenesis

7.1. Endogenous contrast mechanisms

MRI is highly sensitive to motion, a sensitivity that can be harnessed for monitoring the function of the blood vessels without administration of contrast media. Methods such as FLAIR and MR angiography rely on the impact of flow on the apparent R_1 relaxation rate.

Those are effective for detection of motions across time scales of up to a few seconds and translation of blood water across centimeters. Complementary methods such as Pulsed Gradient spin echo measurements of diffusion, ADC and IVIM, rely on loss of coherence of magnetization on the XY plane due to incoherent translation associated with diffusion, convection or flow in randomly oriented capillaries, at a scale of microns to millimeters and time scale of seconds [66]. Both approaches detect the water signal and thus reflect plasma motion and provide information complementary to Doppler Ultrasound imaging.

The vascular bed generates extended and continuous structures within all tissues and thus affects its mechanical properties including stiffness and elasticity. The microcirculation was demonstrated to affect the propagation of shear waves and thus can be detected by MR Elastography [67].

Fibrosis and scar formation is often part of the resolution phase of angiogenesis. Fibrosis can be detected as the desmoplastic reaction in cancer, as well as the progressive damage in

hypovascular regions of the heart. Collagen deposition in fibrotic regions can be detected by chemical exchange saturation transfer and magnetization transfer [68,69].

The susceptibility changes associated with release of oxygen from hemoglobin provides the widely popular BOLD contrast, which can be used as surrogate for detection of cognitive function via local changes in blood oxygenation [70,71]. The same contrast mechanism can be used for detection of changes in vascular function and maturation (ie increased vasoreactivity) during angiogenesis [72,73] or for detection of maternal to fetal oxygen transport across the placenta [74].

The effects of deoxyhemoglobin on susceptibility can be detected by SWI with particular sensitivity to veins and capillaries [75–77]. While deoxyhemoglobin generates $T2_*$ contrast, reporting on intravascular hypoxia, elevated tissue oxygenation can be detected through the effects of dissolved oxygen on T1 contrast (TOLD contrast; [78]). Using a combination of both contrast mechanisms upon exposure to hypoxia to hyperoxia it is possible to derive apparent hemoglobin dissociation values, showing the difference between fetohemoglobin and adult hemoglobin, and map oxygen transport across the placenta [74].

7.2. Contrast enhanced imaging of angiogenesis

Dynamic contrast enhanced MRI using low MW Gd chelates, is widely used for detection of tumors. Contrast enhancement is due to enhanced vascular leak and accumulation of the contrast material in the interstitial space. Pharmacokinetic analysis of contrast enhancement can aid in tumor detection, prognosis, differentiation of benign and malignant lesions, and monitoring response to therapy [79–81].

Permeability of blood vessels to plasma proteins is one of the hallmarks of angiogenesis. Classically, this was measured by extravasion of the albumin binding dye Evans Blue. An MRI biomarker revealing such permeability is provided in the preclinical analysis of the dynamics of accumulation of albumin covalently decorated with multiple GdDTPA groups. Albumin-GdDTPA is a blood pool agent with a long lifetime in circulation and very slow clearance. In angiogenic regions it extravasates to the interstitial extracellular space to create prolonged signal enhancement thus providing a sensitive measure of angiogenesis [82–85]. Its application for clinical imaging of cancer angiogenesis was extensively reviewed [91].

Marrying the ease of delivery of low MW contrast media, with the pharmaco-kinetic advantage of high MW blood pool agents, can be achieved with the use of albumin binding probes such as (MP-2269 and MS-325; Fig. 1) [1]. Using these probes extends the clearance time and enhances the selectivity for detection of a breach in the patency of the vascular wall.

Similar to protein based contrast media, nanoparticles can also be used for detection of the enhanced permeability of angiogenic blood vessels. Such nanoparticles can include dendrimers [92,93], iron-oxide magnetite based nanoparticles [94] and liposomes decorated or loaded with MR detectable payload [95]. By linking targeting moieties to the contrast media, it is possible to highlight endothelial cell surface markers that are enriched during angiogenesis. This approach was applied predominantly for targeting the αVβ3 integrin

[36–40]. Ferumoxytol has been applied for vessel size mapping of angiogenesis in brain tumors [96].

8. Cellular tracking of angiogenesis

Angiogenesis occurs by local proliferation of resident endothelial cells, as well as by recruitment of bone marrow derived endothelial progenitor cells. Thus angiogenesis can be enhanced, for example in hypoxic poorly perfused tissues, by delivery of endothelial progenitor stem cells. Tracking exogenously delivered endothelial progenitor cells can be achieved by MRI by labeling of the cells with detectable contrast media, most often iron oxide nanoparticles, prior to their delivery [97–105]. Such labeling is diluted with cell death or with cell proliferation, and thus there is an advantage to develop reporter genes that can be genetically encoded to be expressed by the cells. Indeed, endothelial expression of ferritin as a reporter gene for MRI was demonstrated in transgenic mice [106]. Another approach included expression of biotinylated tagged protein on the surface of endothelial cells driven by the Tie2 promoter, and detection using avidin labeled contrast probes, showing vascular development in embryos and in tumors [107] [108].

9. Imaging angiogenesis by other modalities

Angiogenesis is an attractive target for imaging by most modalities. Clinical imaging of angiogenesis was demonstrated for contrast enhanced CT, nuclear imaging and ultrasound. Contrast enhanced CT reveals the architecture of blood vessels and their reorganization on tumors [109]. CT is also valuable for analysis of three dimensional vascular casts [110,111]. Such data sets are valuable for the development of algorithms for morphometric analysis of vascular beds. Nuclear imaging (PET and SPECT) provides molecular measures of angiogenesis relying on molecular biomarkers, in particular targeting VEGF receptors and endothelial cell surface integrins [112–115].

Ultrasound has long been a modality of choice for point of care analysis of the vasculature, particularly for cardiovascular and prenatal screening. The recent advancements in Super resolution US offer significant potential for detection of vascular remodeling and its impact on vascular structure and function [116]. An interesting companion technology in opto-acoustic imaging in which light is applied for generation of ultrasound signal. Multispectral opto acoustic imaging (MSOT) is endogenously sensitive to blood oxygenation and can be applied for mapping deoxyand oxyhemoglobin content in blood vessels as well as the distribution of contrast media [117,118].

In addition to the tools listed above, significant progress in preclinical analysis of angiogenesis was made possible by Intravital microscopy, showing cell migration, endothelial sprouting, association with stroma and immune cells and remodeling of the extracellular matrix [58,119–124]. Another interesting modality for imaging superficial angiogenesis is optical coherence tomography, which offers high resolution view of tissue anatomy and the vasculature using endogenous contrast for depth of up to 3 mm [125].

10. Outlook

Angiogenesis biomarkers are proven to be highly valuable in early detection of pathological processes, and can thus be used for aiding biopsy and surgical interventions. With better understanding of the underlying biology, angiogenesis based imaging readouts could aid in diagnosis and monitoring of disease progression as well as response to therapy

Funding

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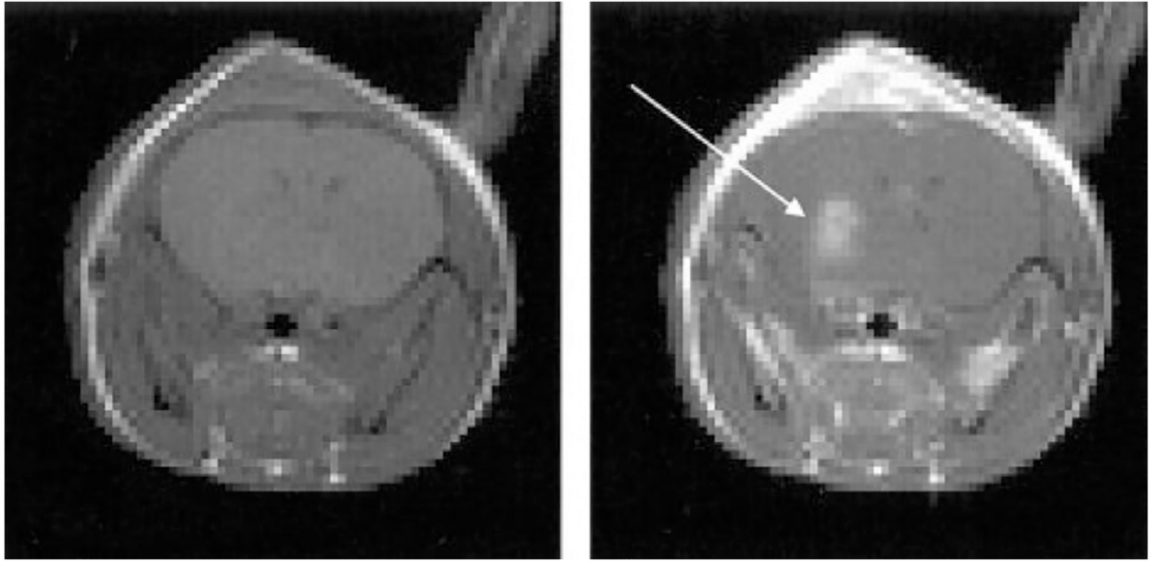
Fig. 1.
Vascular permeability is one of the hallmarks of angiogenesis. Enhanced permeability of the vessels, detected using albumin binding contrast media, enabled early detection of mouse glioma tumors (Reproduced from Magn. Reson. Med. [1]).