Journal of Fundamental and Applied Sciences

ISSN 1112-9867

Available online at http://www.jfas.info

Research Article

Special Issue

ANGIOGENESIS AND HELMINTHS

F. Shariati[1]* , J. L. Pérez-Arellano[2] , J. Lopez-Aban[3] , A. M. Alvarez[3]

[1]Department of Pathobiology, Laboratory of Parasitology, Faculty of Veterinary, Zabol University, Zabol, Iran

[2]Infectious Diseases and Tropical Medicine Unit, Department of Clinical and Surgical Sciences, University of Las Palmas de Gran Canaria, Plaza Dr Pasteur s/n, 35080 Las Palmas, Spain

[3]Laboratory of Immunology and Molecular Parasitology, Faculty of Pharmacy, University of Salamanca, Spain

Published online: 15 May 2016

ABSTRACT

The studies about the role of angiogenic and antiangiogenic factors in the biology of tumor growth and development of metastases are most abundant in the literature. However, both the generation and inhibition of new vessel formation plays an important role in other pathophysiological processes like ischemia, infection and inflammation.

Firstly, we briefly point out the basic concepts of angiogenesis and vasculogenesis, as well as their role in neoplastic and non-neoplastic diseases.

In addition, we study the characteristics of the two major angiogenic factors: vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2). Specifically, the structural features of the above factors and the biological mechanism of action will be indicated. Also, antiangiogenic factors as endostatin, a potent inhibitor of endothelial cell proliferation, migration, angiogenesis and tumor growth will be studied.

Finally, we discuss the role of angiogenic and antiangiogenic factors in the pathogenesis of helminthic diseases. Until now, only very little information has been found and virtually confined to infection with *Schistosoma*spp, filarial species, *Taeniasolium* and *Trichinella* spp.

Author Correspondence, e-mail: fariborzshariati@yahoo.co.uk

doi: http://dx.doi.org/10.4314/jfas.v8i3s.319

For this reason, author interested to study more about parasites and angiogenesis, probably relationship between them, could be open a good way for prevent and treatment of parasite diseases and maybe cancer.

Keywords: Angiogenesis, helminths

INTRODUCTION

Angiogenesis, the process of new blood vessel formation from pre-existing ones, plays an important role in various physiological and pathological conditions, including embryonic development, wound repair, inflammation, and tumour growth. Uncontrolled release of angiogenic growth factors and alteration of the production of natural angiogenic inhibitors, with a consequent modification of the angiogenic balance, are responsible for the uncontrolled endothelial cell proliferation that takes place during tumour neovascularization and in angiogenesis dependent diseases [1].

Animal cells need oxygen and nutrients for their life and are there located within 100-200 µm of blood vessels with a limit for oxygen. For each organism that growth beyond this size, they must recruit new blood vessels by vasculogenesis and angiogenesis. Undoubtedly blood vessels are essential for growing tumours; metastasize to another organ and also for treatment and deliver drugs to all regions of atumour in effective quantities [2].

2. Angiogenesis and tumours

In the initial stages of malignant tumours there is a balance between the proliferation of neoplastic cells and their destruction, by both apoptosis and immune control. When the primary tumour reaches a size limit, the local concentration of oxygen decrease and then cells produce angiogenic factors. Moreover, tissue destruction leads to the next release of anti-angiogenic substances. Given that the average life of anti-angiogenic factors is greater than the stimulant, initially tumour growth and metastasis development is controlled. However, when the balance is altered in favour of pro-angiogenic activity, takes place the formation of new vessels with the consequences noted in following sections.Pro-angiogenic factors include several molecules released by parenchymal or inflammatory cells in response to mechanical factors, metabolic such as hypoxia and acidosis or immune response. Moreover, tissue destruction leads to generation of molecules with anti-angiogenicpotential. The predominance of angiogenic factors leads to the formation of new blood vessels from endothelial precursors both local and mobilized from the bone marrow [3].

Tumourangiogenesis involves both blood vessels and the lymphatic’s vessels. Regarding to blood vessels can be observed differences in comparison with the normal vasculature. Thus,

from a macroscopic point of view, the distribution is much disorganized with dilated tortuous vessels, an irregular diameter and excessive branching and shunts. Microscopically, the endothelium has numerous openings (fenestrate endothelial, vesicles, trans-cellular holes), are widened intercellular junctions and basement membrane is discontinuous or absent. The smooth muscle surrounding the endothelial cells does not contract in response to normal stimuli, which limits the use of vasoconstrictors in antitumor treatment. The main alterations of lymphatic's vessels were compression of the localized within the tumour and dilation of those located in the periphery. These enlarged lymph vessels can pick neoplastic cells derived from the surface of the tumour and thereby facilitate lymphatic metastasis. Therefore, the angiogenesis is a requisite not only for continued tumour growth, but also for metastasis.

3. Angiogenesis in non-neoplastic diseases

Inflammation and hypoxia contribute to angiogenesis in non-neoplastic diseases. In a healthy adult, endothelial cells of blood vessels are in a quiescent state. In the presence of hypoxia or inflammation vascular remodelling occurs with formation of new vessels. One aspect of particular interest is that angiogenesis in non-neoplastic is not like as well as the neoplastic vessels, that lead to the formation of blood vessels with a normal structure and function.

Hypoxia is therefore a very important stimulus of angiogenesis as other biological processes that attempt to restore normal tissue oxygenation. The basic mechanism is the activation of a protein called HIF-1 (hypoxia-inducible factor 1). HIF-1 is a hetero-dimeric protein formed by the junction of two subunits (HIF-1α and HIF-1β).

As the previous data, angiogenesis changes such as excess or deficiency have been observed in multiple diseases, where hypoxia or inflammation plays an important role. In particular there have been changes in angiogenesis in various types of systemic diseases, both autoimmune diseases (eg. rheumatoid arthritis, Systemiclupus erythematosus, systemic sclerosis) [4], metabolicallydiseases (diabetes mellitus) [5] or haematological diseases (Castleman disease) [6]. Moreover, modifications in angiogenesis have seen detected in localized diseases: gastrointestinal tract (eg. Crohn's disease) [4], eyes (age-related macular degeneration) [7], central nervous systemand respiratory diseases [8] or kidney diseases (glomerulonephritis) [9].

4. Angiogenic and anti-angiogenic factors

In condition normal, most blood vessels in an adult organism remain quiescent, to maintain ability to divide in response to stimulus and result in angiogenic process. The positive regulatory molecules responsible of angiogenesis are:Vascular endothelial growth factor (VEGF), Platelet Derived Growth Factor (PDGF), Fibroblast growth factor (FGF),Epidermal

growth factor (EGF), Transforming growth factor (TGF)Matrix metalloproteinases (MMP's), G. TNF (Tumour necrosis factor) and Angiopoietins.

4.1 Vascular endothelial growth factor(VEGF)

Structure and function:

The vascular endothelial growth factors (VEGF) are pleiotropic polypeptides produced by different cell types, including eosinophil [10]. VEGF also known as vascular permeability factor (VPF), is a heparin binding protein and its level is increased in various tumours.`More studies have been carried out about structure and function of these molecules.

The VEGF belong to the VEGF-PDGF (platelet-derived growth factor) super-gene family characterized by 8 cysteines residues are at the same position. 2 out of 8 cysteines generate intermolecular cross-linking, and other 6 cysteines make 3 intra-molecular bands to form 3 loop structures[11].

Among angiogenic factors identified in humans, vascular endothelial growth factor-A (VEGF-A) appears to mediate the basic signalling of angiogenesis which often referred to as simply VEGF.

VEGF is a protein which promotes angiogenesis in chronic inflammation, healing of wounds and tumours. Gene encoding the human VEGF consists of 8 exons and 7 introns. Alternative splicing of VEGF gene results in 4 different isoforms VEGF 121, VEGF165, VEGF 189, VEGF 206 and less frequent spliced isoforms are VEGF 145 and VEGF 183. First 26 AAs in VEGF constitute signalling peptide. The most frequent isoform is VEGF 165 which is a homodimer and has a molecular mass of 45 kD [12].

Hypoxia is one of the important factor inducing VEGF expression.Hypoxia induced transcription of VEGF mRNA is mediated by the hypoxia inducible factor -1 (HIF-1), the binding site of which is located in the VEGF promoter region [13].

VEGF family and related receptors consist ofVEGF A (VEGF), VEGF B, VEGF C, VEGF D, VEGF E and placental growth factor (PIGF) and conclude three tyrosine kinase receptors VEGF R1, VEGF R2, VEGF R3.Like all RTK, VEGF receptors are transmembrane proteins with a single transmembrane domain. Extracellular region are formed by seven immunoglobulin-like domains. Intracellular region exhibits tyrosine kinase activity and separated to two fragments (TK1 and TK2) by an inter kinase insert. VEGF R2 is located in endothelial cells and is the main receptor for the vasculogenic and angiogenic effects of VEGF (14).

Among the inflammatory mediators associated with the production of VEGF are oxygen free radicals [15] and nitric oxide [16]. Finally, several kinds of genetic alterations present in

tumour hereditary diseases or associated with overproduction of VEGF. The best characterized are associated with p53 mutations, the gene encoding the protein of von Hippel-Lindau and PTEN (Phosphatase and Tensin homolog deleted on chromosome 10).

Numerous studies have shown the importance of the expression and function of VEGF in physiological and pathological angiogenesis.

VEGF has endothelial cell mitogenic activity and stimulates growth and proliferation of endothelial cells [8].VEGF also regulate and stimulate permeability, with an effect 50,000 times more than vasoactive effect of histamine. Several studies have shown that VEGF has an important role to prevent the apoptosis of endothelial cells [15].

VEGF has been associated with pathologic angiogenesis associated with tumors, rheumatoid arthritis, and retinopathy of prematurity and other disorders. Inhibition of expression of VEGF has reduced pathological vessel formation in murine models of cancer and other diseases[16].

4.2Fibroblast Growth Factor-2 (FGF-2)

FGF-2 or basic FGF (*fibroblast growth factor*) represents the best-characterized member of the larger family of heparin-binding growth factors. FGF-2 is a potent angiogenic molecule in vivo and in vitro stimulates smooth muscle cell growth, wound healing and tissue repair [17]. In addition, FGF-2 may stimulate hematopoiesis and may play an important role in the differentiation and/or function of the nervous system, the eye and the skeleton.

FGF-2 was firstly identified as a 146-amino acid that was later found a represent toproteolytic product of the primary 18 kDaheparin binding protein. Larger forms of FGF-2 have been identified with 22, 22.5, 24 and 34 kDa, resulting from alternate CUG-translation start sited. FGF-2 contains four cysteine residues with no intra-molecular disulfide bands, a large number of basic residues with an isoelectric point of 9.6 and two sites that can be phosphorylated by protein kinases A and C, respectively [18].

One of the best characterized activities of FGF-2 is its ability to regulate the growth and function of vascular cells such as endothelial and smooth muscle cells. FGF-2 has been implicated in the development and growth of new blood vessels (angiogenesis) and in the pathogenesis of vascular disease such as atherosclerosis **(Figure 1)**. Generally, activity of FGF-2 has been attributed to the intrinsic tyrosine kinase activity of its receptors. However, some study has indicated that FGF-2 can stimulate the dephosphylation of the cell surface HSPG syndecan-4, in the absence of its receptors.

5. Antiangiogenic factors

Angiogenesis inhibitors are substances that inhibit the growth of new blood vessels. Angiogenesis inhibitors can be endogenous including proteins or fragments of proteins that

are formed in the body or exogenous such as drugs or dietary components. The different endogenous angiogenesis inhibitors can be referred are Interferon, TIMP (Tissue Inhibitor of metalloproteinase), Interleukins, Angiostatin and Endostatin.

1. Interferon**:**The interferon is the member of glycoproteins, which has different subtype of interferon (α, β, γ) which directly or indirectly inhibit the tumour angiogenesis and growth.

2. TIMP (Tissue Inhibitor of metalloproteinase): The TIMP (type 1 y 2) inhibits neovascularisation by inhibiting the breakdown of the surrounding matrix.

3. Interleukins: The interleukins play a double function by the particular structure such that IL1 is a cytokine secreted by activated macrophages, is able to induce angiogenesis by increased expression of angiogenic factors, while IL12 has function suppressing the expression of VEGF mRNA, inhibiting proliferation rate in human tumours, promote apoptosis and ultimately reduce the density of tumour vessels [19].

4. Angiostatin:It is a 38 kDa specific inhibitor of endothelial cell proliferation, is an internal fragment of plasminogen containing at least three of the kringles of plasminogen. Angiostatin was isolated from sub-clone of Lewis lung carcinoma in which the primary tumour inhibited the growth of its metastases. Angiostatin, generated by the primary tumour, was demonstrated to potently inhibit angiogenesis. Really, systemic therapy with angiostatin led to the maintenance of metastases in a microscopic dormant state defined by a balance of apoptosis and proliferation of the tumour cells.

5. Endostatin: Endostatin is a 20 kDa C-terminal cleavage product of collagen XVIII which belongs to the multiplexin family and is characterized by multiple triple-helix domains and interruptions.

The generation of endostatin from collagen XVIII is catalyzed by proteolytic enzymes such as cathepsin L and matrix metalloproteinases (MMPs).The endostatin inhibits the binding of VEGF to endothelial cells by binding directly to receptors of VEGF. Therefore, the complex (Endostatin-receptor VEGF) blocks tyrosine phosphorylation and suppress mitogenic effect of VEGF[20].

6. Angiogenic and helminthic diseases

Although the investigation about angiogenesis and tumor come back nearly 100 years ago, but there is a little information about the role of angiogenesis and angiogenic factors in helminthiasis, both in humans and in experimental models.Angiogenic factors are produced either by the parasite or the host, which can stimulate neovascularization through a number of different mechanisms (**Figure 2**).

As an example, has been demonstrated that nematode parasite *C. elegans* encodes a factor, able to binding mammalian VEGF receptors and inducing angiogenesis[21]. This is named *C. elegans* pvf-1 gene that codifies a PDGF/VEGF-like factor with a biochemical properties similar to vertebrate PDGF/VEGF growth factors. In addition, pvf-1 binds to the human receptors VEGFR-1 (Flt-l) and VEGFR-2 (KDR) and is able to induce angiogenesis.

The mechanisms related with host molecules can be divided into three categories; first of all, may be more important, potent angiogenic proteins such as vascular endothelial growth factors (VEGF) and the fibroblast growth factor (FGF-2) induce angiogenesis directly, by stimulation of endothelial cell proliferation, migration and differentiation into vascular tubes. Second, other angiogenic factors, such as interleukin-1, promote angiogenesis indirectly by stimulating inflammatory cells to produce VEGF. And third, angiogenic proteins such as heparinise are proteolytically cleaved, and the released peptides stimulate components of the host's immune system, which in turn stimulate the production of other angiogenic factors such as VEGF and FGF-2 [22]. Finally, some angiogenic factors stimulate other mechanisms involved in the final lesions. In fact, experimental data suggest that hypoxia in relation to VEGF may stimulate proliferation of synthesis of collagen type1 in activated myofibroblast-like rat hepatic stellate cells [23]. They have shown VEGF and angiopoitin 1 (Ang-1) can operate as hypoxia-dependent, autocrine and paracrine factors able to stimulate nonoriented migration and chemotaxis of human myofibroblas-like rat hepatic stellate cells (HSC/MFs) through the activation of (Ras/Erk) signaling.

In practice, the main information about angiogenesis and angiogenic factors in helminthic diseases is limited to infections caused by *Schistosoma*spp, filarial, *Taeniasolium* and *Trichinella* spp.

Schistosomiasis is infections caused by different species of the genus *Schistosoma*. With the exception of cercarial dermatitis and the Katayama syndrome, the pathogenic basis of schistosomiasis is the formation of granulomas around parasite eggs.Although information is scarce in the literature, we note that in the initial stages of schistosomiasis, there is a stimulation of angiogenesis. Thus, it has been clearlydemonstrated by histological and immunohistochemical techniques the presence of angiogenesis in several experimental models of schistosomiasis[24,25,26]. In this context is interesting to note several aspects: (*i*) angiogenesis is an early phenomenon, so in evolutionary phases (such as those has been found in humans) is hard to objectify (Baptista and Andrade, 2005), (*ii*) an aspect importantly demonstrated experimentally in the induction of angiogenesis, is the need for repeated

exposure to the parasite [24] and (*iii*) genetic factors play an essential role in the angiogenic response to the parasite[27,28].

The mechanisms by which *Schistosoma*spp triggers angiogenesis are of various types and have been obtained in experimental studies. Thus, several studies have identified specific *Schistosomamansoni* egg-derived regulatory molecules that include lysophosphatidylserine and prostanoids. Also eggs secrete/excrete additional factors that are capable of stimulating endothelial cell proliferation, migration, p42/44 MAPK phosphorylation and directly, cell sprouting. The effect of this factor is not restricted to endothelial cells, but also it stimulated vascular smooth muscle cells [29]. On the other hand, *Schistosomamansoni* soluble egg antigen (SEA) promotes proliferation, increased tube formation, decreased apoptosis and increased 2-fold messenger RNA for vascular endothelial growth factor (VEGF) of human umbilical vein endothelial cells (HUVECs) [30]. These findings suggest that products secreted by *Schistosoma* eggs may promote angiogenesis within hepatic granulomas by up-regulation endothelial cell VEGF. Also,*Schistosoma*eggs are able to attach to endothelium [31] and indirectly promote angiogenesis through hypoxia and inflammatory response. The main host-derived initiators of this inflammatory response include the early inflammatory cytokine, tumour necrosis factor-α (TNF- α) and the endothelial cell-adhesion molecule, intercellular adhesion molecule-1 (ICAM). At later stages, is developed periportal fibrosis by a mechanism that lymphocytes able to increased levels of profibrotic molecules that include TGF-β and IL-4 [24]. Finally, extravasation of the egg into the surrounding tissue and disruption of the portal stroma causes the migration of inflammatory cells to the site of egg deposition[32].The pre-existing portal stroma, showing normal CD34-immuno-reactivity, is disrupted completely into and around the granulomas and is only preserved closely near to the portal vein and bile duct with modulation of basement membrane components, proteoglycans, collagen and fibronectin imbalancethe connective stromal tissue matrix, has been described previously in schistosomal granulomas. Proteolysis of the dense extracellular matrix by collagens and matrix metalloproteinases (MMPs), a process proceeding to angiogenesis, seems necessary to allow the development of larger inflammatory reaction, While that the endothelial cell proliferation fraction in a quiescent mature vasculature is 0.01% [2], the presence of multiple proliferating cells in each granuloma shows the dynamic angiogenesis in inflammation induced by *Schistosoma*.

Until now, two groups have studied the role of angiogenic factors in human schistosomiasis and their results are hardly comparable. Tawfeek GM et alevaluated 90 patients with schistosomiasis related to *S mansoni* classified in five groups according to

sonographicstudies: infected lightly, heavily infected, intestinal, early hepatosplenic and periportal fibrosis. When compared with controls, they found that VEGF levels were significantly raised in all schistosomiasis patients groups except lightly infected and intestinal groups. Moreover, the level of VEGF correlated with disease progression from lightly infected to periportal fibrosis patients [33]. In a different study design, Toledo and colleagues measured serum levels of VEGF in patients with schistosomiasis with or without portal hypertension. These authors not found significant differences between both groups, although the average values in the group with portal hypertension were younger, a fact that coincides with low levels of VEGF detected in patients with cirrhosis from other causes[34].

In our experiment, VEGF protein was detected in sera of healthy people, patients diagnosed of schistosomiasis, filariasis and hookworms infections. Patient diagnosed with schistosomiasis only showed significant differences in VEGF level in compared with healthy people. In uninfected group were used mice infected with *S. Mansoni*, mice infected and treated with endostatin. In these cases were analyzed obtained data and IgG, IgG1 and IgG2a specific antibodies. The VEGF and FGF2 expression were detected by RT-PCR in liver and intestine. Mice treated with endostatin showed significant differences in eggs recoveries in liver and IgG2a antibodies detection in compared with infected mice group. Finally, the effects of the cercarial and adults *S. mansoni* antigens on the VEGF and FGF2 stimulation were evaluated. Macrophages were obtained by bronchoalveolar lavage (BAL) from Wistar rats. Cells were cultured at different concentrations of antigens (0.1-50 µg/ml), and their expression were determined by RT-PCR. Cells stimulated with 50µg/ml of cercarial of *S .mansoni* antigens, expressed VEGF and FGF2 [35].

Filariasis is diseases related with the infection of several genus and species of nematodes (*Wuchereriabancrofti, Brugiamalayi, Brugiatimori, Onchocerca volvulus, Loa loa, Mansonella Perstans, Mansonella ozzardi*and *Mansonella streptocerca*). Altered angiogenesis has been described in only two types of filarial diseases: lymphatic filariasis[36]and onchocerciasis. Clinical lymphatic filariasis (and specifically infections related with *W. bancrofti)* are characterized with lymphoedema, lymph vessel dilation, lymph extravasation and, in some cases, the development of elephantiasis. There is some evidence of the role of angiogenic factors (and specifically of the family of VEGF) in the pathogenesis of lymphatic filariasis. Thus, in a longitudinal study in 63 Polynesian patients living in a hyperendemic focus of *W. bancrofti*, chyluria was associated with increased vascular endothelial growth factor (VEGF) levels, whereas elephantiasis presented a highendothelin-1 (ET-1) profile [37]. On the other hand, host genetics is related with the clinical evolution of

lymphatic filariasis. Specifically, in a cohort of lymphatic filariasis patients from Ghana, three VEGF-A promoter polymorphisms were examined [38]. The authors found that C/C genotype at -460 was significantly higher in hydrocele patients and in patients with high serum VEGF levels. Finally, in a cohort of bancroftiand filariasis in Ghana, serum VEGF-C and sVEGFR-3 were elevated at basal evaluation [39]. Doxycycline-treated patients (for *Wolbachia*spp eradication) decrease VEGF-C and sVEGFR-3 at a level close to that of endemic normal values, with amelioration of supratesticular dilated lymphatic vessels and with an improvement of lymphatic pathology.

Onchocerciasis is characterized by two types of clinical manifestations: subcutaneous nodules (microfilarial-related), skin and ocular lesions (microfilarial-related). The*O volvulus* nodules in perfusion studies have different patterns of angiogenesis [40]. Small nodules had an extensive blood supply, diffusely distributed throughout the nodule matrix and in close association with the coils of the worms. In bigger nodules, the central area appeared denser and intense vascularisation appeared to be more peripheral; in the largest nodules the central core was not well vascularised, but a band of heavy vascularisation was seen at the margin of the core, fed by superficial vessels and in close contact with worm coils. It is supposed, one derived *O volvulus* protein (*Ancylostoma* secreted protein homologue) can contribute to abnormal angiogenesis [41].

Neurocysticercosis is a common central nervous system (CNS) infection caused by *Taeniasolium*metacestodes. In this infection is well-documented the importance of the granulomatous response in their pathogenesis. A small series of eight patients with neurocysticercosis subjected to craniotomy for histological and immunohistochemical analysis, shows dying parasite surrounded by a mature granuloma with associated fibrosis, angiogenesis and an inflammatory infiltrate. The most abundant cell types were plasma cells, B and T lymphocytes (Th1), macrophages, and mast cells [42].Moreover, an increased angiogenesis has been observed in animal models of neurocysticercosis[43].

Trichinellosis is a nematode infection in which primarily affects striated muscle cells. Larvae of *Trichinella*spp initiate the transformation of myocytes into nurse cells that become surrounded by elaborate networks of blood vessels. In mice experimentallyinfected by *Trichinella*spp several vessel abnormalities were detected[44]. Thus, vascular complexes were found only around infected myocytes and were characterized by large circumferential vessels that give rise to the smaller channels of the retes. The secondary vessels vary widely in caliber and are distributed in a random fashion. Three types of network were found: simple, complex, and hyper-complex. They were distributed normally with the complex network. The

comparison of the structure of the baskets with that of vessels in surrounding uninfected muscle strongly suggests that the vascular network are the result of de novo angiogenesis induced during the infection. In this setting, excretory/secretory products of larval *Trichinellaspiralis*and *Trichinellapseudospiralis*have been related with degenerative/ regenerative muscular changes and angiogenesis [45].

Study on the *Trichinella* in our lab have shown the effect of different *Trichinella* L1 antigens from one encapsulated (*Trichinellaspiralis*) and one non-encapsulated (*Trichinellapseudospiralis*) on the expression of VEGF and basic Fibroblast Growth Factor (FGF2) and investigation on the relationship between the production of nitric oxide (NO) and angiogenic mediators.Our studydemonstrate that the macrophages are able to produce and to release not only VEGF but also FGF2 in response to antigens of encapsulated species like *T. spiralis*, in a dose-dependent manner. Gene expression of VEGF was determined by RT-PCR and protein expression measured by ELISA. Nevertheless, non-encapsulated species likes *T. pseudospiralis*werenot able to induce the expression of these angiogenesis factors. The larva penetrates the muscle cell, grows in it and destroyed myofibrils. The satellite cells that surround the cell with muscle fibre undergo morphological changes transforming into nurse cells. Previously it has been demonstrated that the nurse cells are able to produce VEGF during the infection by *T. spiralis* [46]. Our work, demonstrate that inflammatory cells that surround the injured muscle fibre contribute in the production of angiogenic factors. Probably, both cell types contributed to the development of the capsule of this species.As NO is an inductive factor for VEGF production [47]we evaluated whether the inhibition of NOS, by using the specific inhibitors L-NAME and L-canavanine, modified the effect of antigens of *Trichinella* on the production of angiogenesis factors. This study demonstrates that the effect of the antigens of *T. spiralis* does not depend on NO [48].

Strongyloidiasis is a genus of parasitic nematodes which includes some 50 species of obligatory parasites of vertebrates. Two species of *Strongyloides*whichinfect humans are *S. stercoralis*and *S. fuelleborni*[49]. In healthy individuals, infection with *Strongyloides*can be clinically in apparent or can lead cutaneous, gastrointestinal or pulmonary symptoms. However, *Strongyloides*infection in immunocompromised individuals (e.g., corticosteroid use and human T lymphotropic virus type I infection) can result in disseminated strongyloidiasis, in which worms move beyond the confines of the gut into other organs [50].

The life-cycle of *Strongyloides*is complicated and available data are mainly obtained in experimental infections (S. *ratti* and *S venezuelensis*) [51,52]. Usually, hosts become infected when free-living infective third stage larvae (L3sv) penetrate the skin and/or digestive

mucosal surfaces. These larvae access to blood vessels and are dispersed to many organs, being passage through the lungs [51]. During this migration L3sv moult to L4 stage and then the adult parasitic worms present in the gut in few days with reproduction commencing shortly thereafter, detected by the presence of eggs and, or larvae in the faeces. A key pathogenic clue of acute infection (and probably of hiperinfection) by *Strongyloides*spp is their dissemination though blood vessels until the access to target organs (mainly lung and gut). However, no data are available on the role of angiogenic factors in the pathogenesis of strongiloidiasis.

Other work in our lab was study the role of different antigens of *Strongyloidesvenezuelensis*on expression/no expression the vascularendothelial growthfactor and fibroblast growth factor using Wistar rat alveolar macrophage cells. Larvae and adult worms decontaminated firstly, and somatic and excretory/secretory antigens of *S. venezuelensis* prepared from them. Alveolar macrophage cells obtained by bronchoalveolar lavage were incubated by different concentrations of antigens (0.1–50µg/ml).The mRNA level of VEGF and FGF2 in macrophage cells detected by RT-PCR. The authors hypothesized that inhibition of VEGF activity by endostatin as a potent angiogenesis inhibitors prevents angiogenesis and decreased disease sign in mice infected by *S. venzuelenesis*. Group of mice CD1 were infected with 3000 of third larvae of parasite. One day before infection two groups of mice received one dose of ED (2.5mg/kg) subcutaneously (sc). In a follow- up experiment, a similar treatment was followed duration 48 hours: first experiment include three group of mice (uninfected group, infected group and endostatin group received only two doses) were sacrificed at 2 days post-infection to assess of lung to study of different sign in the second day of infection and second experiment with three groups as above but group of endostatin received four doses and were sacrificed at 14 day for study and compare effect of endostatin in vivo [53].

7. Angiogenic and others diseases

It is thought that VEGF and its receptor-related molecules are over-expressed in brain tissues of cerebral malaria (CM) patients, secondary of occlusion of micro vessels by parasitized erythrocytes. The increased level of VEGF as well as a potential biomarker can be detectable in biologic sample of these patients[54].

CONCLUSION

The knowledge on the role ofangiogenicandanti-angiogenesis in the biology of the growth of tumour cells and the development of metastasis factors has been major advance

incompressionofthe pathogenesisof many diseases in the last decades. In general, both the uncontrolled release of angiogenesis factors as well as alteration of the natural production of inhibitorsaniogenesisdue to the modification of the angiogenicbalance, are responsible the uncontrolledproliferation ofendothelialcells, such as occurs during the neovascularizationin tumourangiogenesisandassociated diseases. The supposed that, in tumourangiogenesisare involvedbothblood vesselsandlymphvessels. This neovascularisation generated from pre-existing blood vessels and these vascularmodifications lead totheincreased secretionofVEGFandTNF-a secondarytohypoxiaandacidosis in tissue.

The helminth infections are not only a public health hazard that affect patients but also represents an economic problem in animal production and food safety. The information about angiogenesis and angiogenic factors in helminthiasis is scarce and limited to infections caused by some parasites such as *Schistosoma* spp, filarial infections and *Taeniasolium* and *Trichinella* spp and all of these finding are demonstrated by using histological and immunohistochemical techniques in experimental models, In this review, we attempt demonstrate role of angiogenesis factors in helminthiasis infections, which open some way for future research.

Trichinellosis is a widespread parasitic zoonosis caused by the eating of inadequately cooked meat containing the infective larvae of the *trichinella* as nematode genus. In this nematode genus are recognized two main clases: The encapsulates group, such as *T. britovi*, *T. murrelli*, *T.nativa*, *T. nelsoni*, *T. spiralis*, usually live in the muscle tissues as host cells and non capsulated such as *T. papuae*, *T. pseudospiralis*, *T. zimbabwensis*. When *Trichinellaspiralis* is in larval stage, penetrate in the muscle cells especially striated skeletal muscle cell, as host cells for the purpose of larval caregivers. The level of VEGF detect in the area surrounding of nurse cells, although, is unknown still the antigens involved in their mechanism, role of angiogenic factors in this process and relationship between Nitric oxide (NO) production and angiogenesis. The finding of investigation show that host macrophages in murine model able to expression of VEGF and FGF2 with different manner y different quantitative in non-encapsulated and encapsulated *Thrichinella* species. Also, in the pathogenesis of *T.spiralis* antigen, there is no relationship between NO and angiogenic factors.

Other parasite that affects to very many people in the worldwide especially in tropical area is Schistosomiasis. This parasite is trematode specie and its disease encompasses four species intestinal genus Schistosoma and can be damage in several organs secondary to chronic course of illness. In the experimental studies between *Schistosoma* spp and angiogenesis have identified lysophosphatidyl serine and prostanoids derived from eggs of *S.mansoni* that play

as regulatory molecules of angiogenesis. Also, these eggs secrete additional factors that are capable of stimulate proliferation and migration of endothelial cells and phosphorylation of p42/44MAPK.This effect is not limited to endothelial cells, but also induces vascular smooth muscle cells.Moreover, soluble antigens of *S.mansoni* eggs (SEA) stimulate proliferation and formation of new vessels, reducing apoptosis and increasing the expression of the gene for VEGF in human endothelial cells from the umbilical vein (HUVEC). These findings suggest that the products secreted by *Schistosoma* eggs may promote angiogenesis in liver granulomas by overexpression of VEGF. In addition, eggs of *Schistosoma* adhering to endothelium promote angiogenesis indirectly by hypoxia and inflammatory response initiated by TNF-αand ICAM-1. The angiogenesis phenomena occurs in the initial phase of granuloma formation from pre-existing vessels, which propose is the principle mechanism implicated in the pathogenesis. In later stages, periportal fibrosis is developed by a mechanism involving lymphocytes that produce molecules pro-fibroticas TGF-b and IL-4. Finally, the infiltration of eggs causes migration of inflammatory cells to this site.The VEGF level is significantly high in infected patients with schistosomiasis and filariasis in compared with patients diagnosed with other hookworms.

There are a few searches about relationship between concentrations of VEGF in infected patients. Tawfeek et al and our work demonstrated a high level of VEGF in sera of patients infected with parasites such as schistosomiasis, filariasis and hookworms. Moreover, were no significant differences between VEGF levels in patients infected with different subtype of schistosomiasis such as *S. mansoni* and *S. haematobium*.Although, there is no data the using of anti-angiogenic drugs in humans but also, after using Endostatin (anti-angiogenic drug) in infected animal model with schistosoma observed a significant reduction in the number of eggs in the liver and number of granulomas. Also, using of endostatine in infected mice with scistosomiasis showed reduction in the number of adult worms and decrease in formation of lesion, secondary to decrease VEGF secretion. These dates indicate the inhibition of angiogenesis induce a decreasing of hepatic injury and subsequent fibrosis.The involving mechanisms supposed that the cercariae antigens *S. mansoni* are able to stimulate the angiogenic factor (VEGF, FGF2) by exposed alveolar macrophage in murine model.

On the other hand, there is no significant differences in blood cells count (red, white, platelet) both S. mansoni infected mice as mice treated with endostatin. Also human population infected with schistosomiasis, filariasis and hookworm presented consistent eosinophils, which no observed in murine model infected with strongyloidiasis.

Furthermore, there is interested information between angiogenic factors and pathogenesis of Strongyloides. The stongyloides is other genus of parasitic nematodes, specially *S. stercoralis* and *S. fuelleborni* are two species that can be produce several organ affectation such as pulmonary, gastrointestinal and cutaneous organs both in health person and immunosuppresed patients, including in patients with steroid therapy can be produce disseminated infection. Some authors suggested that *S. venezuelensis* and *S. ratti* are appropriate parasite models for the study of *S. stercoralis*. The parasitological examination revealed a significant decrease in egg per gram of faeces, number of collected larvae from lung tissue and number of collected adult females, when CD1 mice infected with *Strongyloidesvenezuelensis* received endostatin, it is C-terminal fragment of collagen XVIII with angiogenesis inhibitor function; Perhaps, these changes might be occurs in relation of decrease of angiogenesis factors such as VEGF and FGF2 directly and indirectly increase of numbers of eosinophils and macrophages respectively. Macrophages and eosinophils are cells that capable to produce multiple potent angiogenic factors including VEGF, FGF2, cytokines factors, chemotactic receptors in infections, tumor situations.

Further, when alveolar macrophage cells obtained by bronchoalveolar lavage were incubated at different concentrations of somatic and excretory ⁄ secretory antigens of *S. venezuelensis*, observed that L3-PBS larvae antigens can be induced angiogenic factors, confirmed by presence of mRNA of VEGF, FGFR1 in stimulated macrophages.

On the other hand, Nitric oxide (NO), is a regulate VEGF expression and therefore angiogenesis process. Alveolar macrophages release NO in response of helminthic antigens, which can be inhibiting by using of L-NAME and L-Canavanine, these are drug with ONSi effect. These dates confirm a positive relationship between angiogenesis factors and NO. Although more research are necessary to assess the role of NO in the strongyloidiasis, but supposed that nitric oxide (NO), in presence of L3-PBS larvae antigen, play as inflammatory mediator.

Although, from 1971, Folkmanproposed ahypothesis the angiogenesisin growth of tumours andmetastasisand thereforetheir blockingmay be one strategyto detecttumour growth until nowdayswe know that theangiogenicfactors produced bythe parasiteorthe hostcan stimulate theneovascularizationthroughseveral mechanisms. An important aspect necessary to generated of angiogenesis is repeated exposure to the parasite and it’s supposed that the genetic factors play a key role in the angiogenic response against helminthes, but also,there is still littleinformation aboutthe role ofangiogenesisandangiogenicfactors inhelminth infections, inso manyhumans andexperimental models andstill manyunanswered questions,it is

supposedthatmoreinvestigationin the futureknowmoreabout the mechanismsof these diseasesremain.

Table 1. Genetic and functional differences of the five VEGF synthesized in mammals
In the mammals, only the first five have biological importance, VEGF-E is a viral protein [Orf-virus (open reading frame, in the genome of Orf virus)-derived VEGF] and VEGF-F a protein derived from snake venom.

Types of VEGF	VEGF-A	VEGF-B	VEGF-C	VEGF-D	PlGF
Chromosome	6p23.1	11q.13	4q34	Xp22.31	14q.24
Isoforms	YES	YES	NO	NO	YES
Receptors	VEGFR1 VEGFR2 NP-1NP-2	VEGFR1	VEGFR2	VEGFR3	VEGFR1 NP-1
Biologic function	Multiple	A little known - Coronary vessels	Lymphangiogenesis	Lymphangiogenesis	Complementary of VEGF-A

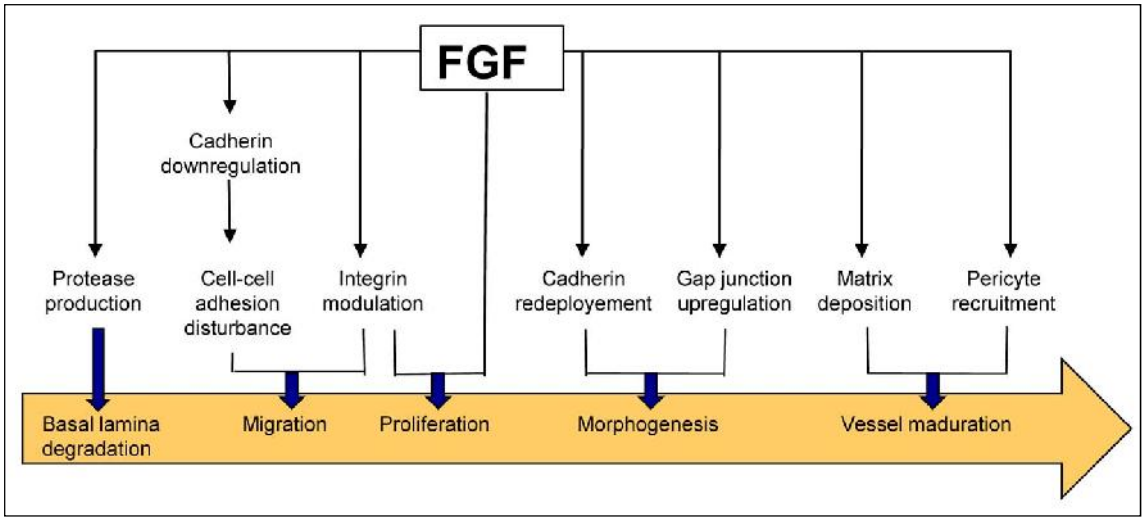

Fig.1. Mechanisms of FGF-2 induced angiogenes, One of the best characterized activities of FGF-2 is its ability to regulate the growth and function of vascular cells such as endothelial and smooth muscle cells. FGF-2 has been implicated in the development and growth of new blood vessels (angiogenesis) and in the pathogenesis of vascular disease such as atherosclerosis.

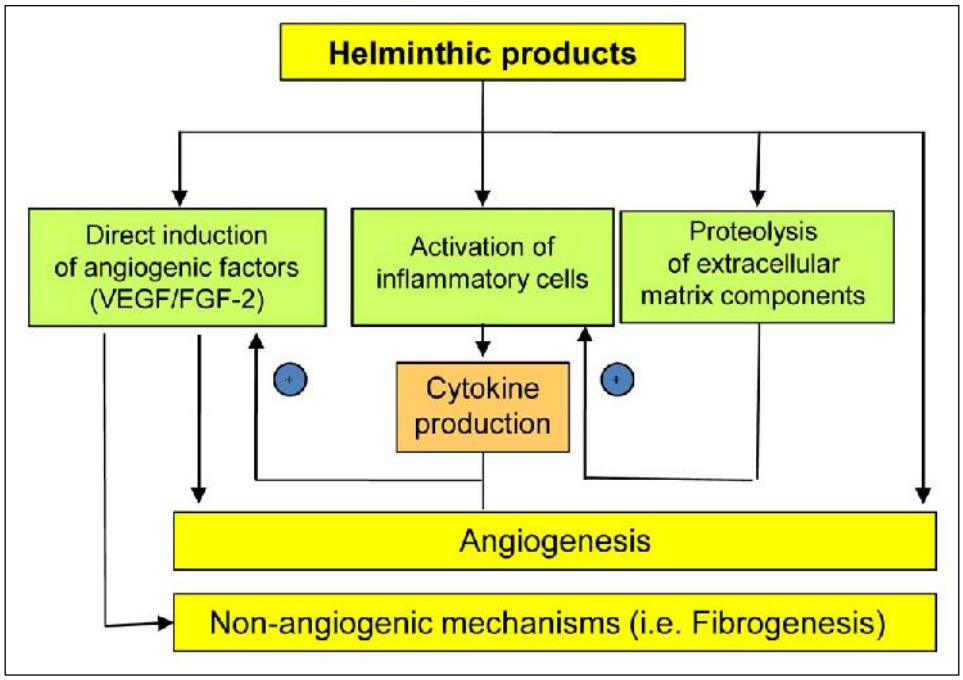

Fig. 2. Helminths and angiogenesis Angiogenic factors are produced either by the parasite or the host can stimulate neovascularization through a number of different mechanisms.

REFERENCES:

[1] Folkman J. Antiangiogenesis in cancer therapy-endostatin and its mechanism of action. Exp Cell Res 2006, 312:594-607

[2] Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000, 407: 249-57

[3] Sathornsumetee S, Rich JN. Antiangiogenic therapy in malignant glioma: promice and challenge. Curr Pharm Des 2007, 13: 3545-58

[4] Carvalho J, Blank M, Shoenfeld Y. Vascular Endothelial Growth Factor (VEGF) in Autoimmune Diseases. J ClinImmunol 2007, 27: 246-256

[5] Crawford TN, Alfaro DV, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. Curr Diabetes Rev 2009, 5: 8-13

[6] Nishi J, Maruyama I. Increased expression of vascular endothelial growth factor (VEGF) in Castleman's disease: proposed pathomechanism of vascular proliferation in the affected lymph node. Leuk Lymphoma 2000, 38: 387-94

[7] Bressler SB. Understanding the role of angiogenesis and antiangiogenic agents in age-related macular degeneration.Ophthalmology 2009, 116(10 Suppl):S1-7

[8] Yadav L, Puri N, Rastogi V, Satpute P, Sharma V. Tumour Angiogenesis and Angiogenic inhibitors: A Review. J Clin Diagn Res 2015, 9: XE01-XE05

[9] Richter AG, Maughan EO, Perkins GD, Nathani N, Thickett DR, 2005. VEGF levels in pulmonary fibrosis. Thorax 2005, 60: 171

[10] Takafumi Yamaguchi, Hirokazu Kimura, Masahiko Kurabayashi, Kunihisa Kozawa, Masahiko Kato. Interferon-gamma enhances human eosinophil effector functions induced by granulocyte-macrophage colony-stimulating factor or interleukin-5. ImmunolLett. 2008, 118:88-95

[11] Shibuya M. Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. Cell StructFunct 2001, 26: 25-35

[12] Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. Biochem Biophys Res Commun. 1989;161:851-58

[13] Mazure NM, Chen EY, Laderoute KR, Giaccia AJ. Induction of vascular endothelial growth factor by hypoxia is modulated by a phosphatidylinositol3-kinase/Akt signalling pathway in Ha-ras-transformed cells through a hypoxia inducible factor-1 transcriptional element. Blood. 1997;90:3322-31.

[14] Karamysheva AF. Mechanism of angiogenesis. Biochemistry. 2008;73:935-48.

[15] Asano-Kato N, Fukagawa K, Okada N, Kawakita T, Takano Y, Dogru M, Tsubota K, Fujishima H. TGF-beta1, IL-1beta, and Th2 cytokines stimulate vascular endothelial growth factor production from conjunctival fibroblasts. Exp Eye Res 2005, 80:555-560

[16] D.J.Hicklin, L.M. Ellis, Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis, J. Clin. Oncol. 23 (2005) 1011-1027

[16] Kimura H, Esumi H. Reciprocal regulation between nitric oxide and vascular endothelial growth factor in angiogenesis. Acta Biochim pol 2003, 50:49-59

[17] Korc M, Friesel RE. The role of fibroblast growth factors in tumor growth.Curr Cancer Drug targets2009, 9:639-651

[18] Casu B, Naggi A, Torri G. Heparin-derived heparansulfate mimics to modulate heparansulfate-protein interaction in inflammation and cancer. Matrix Biol 2010, 29: 442-452

[19] Kim YM, Hwang S, Kim YM, Pyun BJ, Kim TY, Lee ST, et al. Endostatin blocks vascular endothelial growth factor mediated signalling via direct interaction with KDR/Flk-1. J Biol Chem. 2002;277:27872-79.

[20] Lalita Yadav, Naveen Puri, Varun Rastogi, Pranali Satpute, and Vandana Sharma Tumour Angiogenesis and Angiogenic Inhibitors: A Review.J Clin Diagn Res. 2015 Jun; 9(6): XE01–XE05.

Published online 2015 Jun 1. doi: 10.7860/JCDR/2015/12016.6135

[21] Tarsitano M, De Falco S, Colonna V, McGhee JD, and Persico MG. The *C. elegans pvf-1* gene encodes a PDGF/VEGF-like factor able to bind mammalian VEGF receptors and to induce angiogenesis. FASEB J 2006, 20:227-233

[22] Vlodavsky I, Ilan N, Naggi A, Casu B.Heparanase: structure, biological functions, and inhibition by heparin-derived mimetics of heparansulfate. Curr Pharm Des 2007, 13:2057-2073

[23] Novo E, Povero D, Busletta C, Paternostro C, di Bonzo LV, Cannito S, Compagnone A, Bandino A, Marra F, Colombatto S, David E, Pinzani M, ParolaM.The biphasic nature of hypoxia-induced directional migration of activated human hepatic stellate cells.J Pathol 2012, 226:588-97

[24] Caldas IR, Campi-Azevedo AC, Oliveira LF, Silveira AM, Oliveira RC, Gazzinelli G. Human schistosomiasismansoni: immune responses during acute and chronic phases of the infection. Acta Trop 2008, 108:109-117

[25] Ahmed AM, Abbas H, Mansour FA, Gasim GI, Adam I.Schistosomahaematobium infections among schoolchildren in central Sudan one year after treatment with praziquantel.Parasit Vectors2012, 5:108

[26] Andrade ZA, Baptista AP, Santana TS. Remodeling of hepatic vascular changes after specific chemotherapy of schistosomalperiportal fibrosis. Mem Inst Oswaldo Cruz2006, 1:267-72

[27] Van de Vijver KK, Colpaert CG, Jacobs W, Kuypers K, Hokke CH, Deelder AM, Mark EV. The host's genetic background determines the extent of angiogenesis induced by schistosome egg antigens. Acta Trop 2006, 9: 243-251

[28] Smith PM, Shainheit MG, Bazzone LE, Rutitzky LI, Poltorak A, Stadecker MJ. Genetic control of severe egg-induced immunopathology and IL-17 production in murine schistosomiasis. J Immunol 2009, 183:3317-3323

[29] Kanse SM, Liang O, Schubert U, Haas H, Preissner KT, Doenhoff MJ, Dennis RD. Characterisation and partial purification of *Schistosomamansoni* egg-derived pro-angiogenic factor. Mol BiochemParasitol 2005, 144: 76-85

[30] Loeffler DA, Lundy SK, Singh KP, Gerard HC, Hudson AP, Boros DL. Soluble egg antigens from *Schistosomamansoni* induce angiogenesis-related processes by up-regulating vascular endothelial growth factor in human endothelial cells. J Infect Dis 2002, 11: 1650-1656

[31] Reis EA, Azevedo TM, McBride AJ, Harn DA Jr, Reis MG.Naïve donor responses to Schistosomamansoni soluble egg antigens. Scand J Immunol 2007,66:662-670

[32] Coutinho EM, Oliveira SA, Barros AF, Silva FL, Ramos RP. Manson's schistosomiasis in the undernourished mouse: some recent findings. Mem Inst Oswaldo Cruz 2010, 105:359-366

[33] Tawfeek GM, Alafifi AM, and Azmy MF. Immunological indicators of morbidity in human Schistosomiasismansoni: role of vascular endothelial growth factor and anti-soluble egg antigen IgG4 in disease progression. J Egypt Soc Parasitol 2003, 33:597-614

[34] de Toledo CF, Carvente CT, Shigueoka DC, and Borges DR 2009. Endothelial markers in schistosomiasis patients with or without portal hypertension.Dig Dis Sci 2009, 54:1331-1336

[35] Shariati F, Pérez-Arellano JL, Carranza C, López-Abán J, Vicente B, Arefi M, Muro A. Evaluation of the role of angiogenic factors in the pathogenesis of schistosomiasis. Exp Parasitol 2011, 128: 44-9

[36] Pfarr KM, Debrah AY, Specht S, Hoerauf A. 2009. Filariasis and lymphoedema. Parasite Immunol 2009, 31:664-672

[37] Esterre P, Plichart C, Huin-Blondey MO, Nguyen LN. Soluble cellular adhesion molecules, selectins, VEGF and endothelin-1 in patients with Wucheriabancrofti infection and association with clinical status. Parasite Immunol 2005, 27: 9-16

[38] Debrah AY, Mand S, Toliat MR, Marfo-Debrekyei Y, Batsa L, Nürnberg P, Lawson B, Adjei O, Hoerauf A, Pfarr K. Plasma vascular endothelial growth Factor-A (VEGF-A) and VEGF-A gene polymorphism are associated with hydrocele development in lymphatic filariasis. Am J Trop Med Hyg 2007, 77: 601-608

[39] Debrah AY, Mand S, Marfo-Debrekyei Y, Batsa L, Pfarr K, Lawson B, Taylor M, Adjei O, Hoerauf A. Reduction in levels of plasma vascular endothelial growth factor-A and improvement in hydrocele patients by targeting endosymbioticWolbachia sp. in Wuchereriabancrofti with doxycycline. Am J Trop Med Hyg 2009 80:956-963

[40] Trees AJ, Graham SP, Renz A, Bianco AE, Tanya V.Onchocercaochengi infections in cattle as a model for human onchocerciasis: recent developments. Parasitology 2000, 120 Suppl:S133-142

[41] Higazi TB, Pearlman E, Whikehart DR, Unnasch TR. Angiogenic activity of an *Onchocerca volvulusAncylostoma* secreted protein homologue. Mol Biochem Parasitol 2003, 129:61-68

[42] Restrepo BI, Álvarez JI, Castaño JA, Arias LF, Restrepo M, Trujillo J, Colegial CH, Teale JM. Brain granulomas in neurocysticercosis patients are associated with a Th1 and Th2 profile. Infect Immun 2001, 69: 4554-4560

[43] Sikasunge CS, Johansen MV, Phiri IK, Willingham AL 3rd, Leifsson PS.The immune response in Taeniasoliumneurocysticercosis in pigs is associated with astrogliosis, axonal degeneration and altered blood-brain barrier permeability. Vet parasitol2009, 160:242-250

[44] Dabrowska J, Walski M, Grytner-Ziecina B, Machnicka-Rowińska B, Jankowska-Steifer E. [Ultrastructural analysis of capsule and nurse-cell morphology examined seven months after Trichinellaspiralis mouse infection]. Wiad Parazytol 2004, 50:279-284

[45] Nagano I, Wu Z, Takahashi Y. Species-specific antibody responses to the recombinant 53-kilodalton excretory and secretory proteins in mice infected with Trichinella spp. Clin vaccine immunol 2008, 15:468-473

[46] Capo VA, Despommier DD, Polvere RI. *Trichinellaspiralis*: vascular endothelial growth factor is up-regulated within the nurse cell during the early phase of its formation. J Parasitol 1998, 84:209-214

[47] Namba T, Koike H, Murakami K, Aoki M, Makino H, Hashiya N, Ogihara T, Kaneda Y, Kohno M, Morishita R. Angiogenesis induced by endothelial nitric oxide synthase gene

through vascular endothelial growth factor expression in a rat hindlimb ischemia model. Circulation 2003, 108:2250-2257

[48] Shariati, F., Perez-Arellano, J. L., Lopez-Aban, J., Arefi, M., Martinez-Fernandez, A. R. and Muro, A. Trichinella: differential expression of angiogenic factors in macrophages stimulated withantigens from encapsulated and non-encapsulated species. Experimental Parasitology 2009, 123:347–353

[49] Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. Clin Infect Dis 2001, 33:1040-1047

[50] Vadlamudi RS, Chi DS, Krishnaswamy G. Intestinal strongyloidiasis and hyperinfection syndrome. Clin Mol Allergy 2006, 4:8

[51] McHugh TD, Jenkins T, Greenwood R & McLaren DJ. The migration and attrition of Strongyloides ratti in naive andsensitized rats. J Helminthol 1994, 68:143–148

[52] Tsuji N, Ohta M & Fujisaki K. Expression of a 70-kDa heatshock-related protein during transformation from free-livinginfective larvae to the parasitic stage in Strongyloidesvenezuelensis. Parasitol Res 1997, 83:99–102

[53] Shariati, F., Perez-Arellano, J. L., Lopez-Aban, J., El Behairy, A. M, Muro, A. Role of angiogenic factors in acute experimentalStrongyloidesvenezuelensis infection. Parasite Immunology 2010, 32:430–439

[54] Canavese, M., Vascular Endothelial Growth Factor: An Overview AcrossMultiple Disease Conditions.Am J Pharmacol Toxicol 2015, 10 (1): 1.12

How to cite this article:
Shariati F, Pérez-Arellano L J, Lopez-Aban J, Alvarez M A. Angiogenesis and helminths. J. Fundam. Appl. Sci., 2016, *8(3S), 2037-2058.*