

# Angiogenesis and its potential role in the growth and proliferation of pathogens

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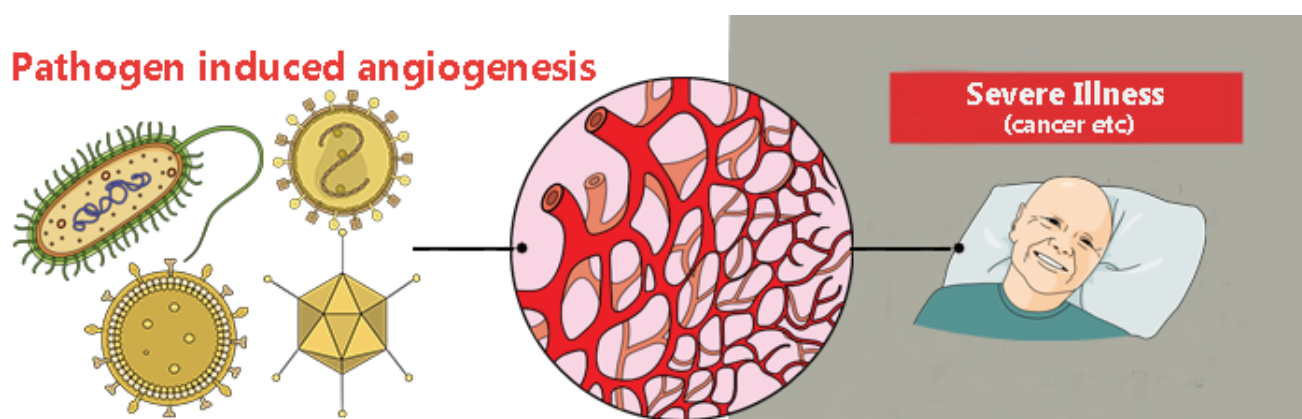
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**Significance | Angiogenesis induced by infection of pathogens**

**Graphical Abstract**



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# Angiogenesis and its potential role in the growth and proliferation of pathogens

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## Abstract

Angiogenesis is an important physiological process by which new blood vessels form from pre-existing vessels. Other than being an important physiological process in embryo development, wound healing, and in response to ovulation (Adair and Montani, 2010a), it also contributes to the pathology of a number of diseases. Several pathogens, including bacteria, mycobacteria, and viruses, induce angiogenesis during their infection and their pathogenesis within the human body. The excessive angiogenesis induced by the infection of these pathogens usually contributes to the seriousness of the disease. Several bacteria of the *Bartonella* genus induce angiogenesis during their infection of the human body, as well as *Helicobacter pylori* and *Mycobacterium tuberculosis*. Viruses such as the hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma-associated herpesvirus (KSHV), and orf virus also triggers angiogenesis during their infection. The principal mode of angiogenesis activation is via the stimulation of inflammatory mediators that lead to the increase of VEGF, which is the primary signalling molecule for angiogenesis activation. An increased level of VEGF in the plasma is common in a number of pathogen-induced diseases. The state of hypoxia that resulted from infections activates HIF-1, a transcription factor for VEGF expression (Forsythe et al., 1996). Other important angiogenesis mediators that were

activated during pathogenesis include cytokines like IL-6 and -8, angiogenins, as well as the matrix metalloproteinases (MMPs). Hence, targeting angiogenesis may have a potential therapeutic value in treating or managing pathogen infection.

**Keywords:** angiogenesis, HIF-1, Bartonella, Mycobacterium tuberculosis, hepatitis, herpesvirus, orf, Helicobacter pylori

**Abbreviations:** VEGF, vascular endothelial growth factor; HIF-1, hypoxia-inducible factor; IL-6, interleukin-6; IL-8, interleukin-8; IL-12, interleukin-12; vIL-6, viral interleukin-6; Ang-2, angiopoietin 2; COX-2, cyclooxygenase 2; MMP-1, matrix metalloproteinase 1; MMP-2, matrix metalloproteinase 2; MMP-3, matrix metalloproteinase 3; MMP-9, matrix metalloproteinase 9; MMP-14, matrix metalloproteinase 14; TNF $\alpha$ , tumour necrosis factor; NF $\kappa$ B, nuclear factor kappa-B; PlGF, placental growth factor; CXCR2, chemokine (C-X-C motif) receptor 2; ADM, adrenomedullin; IGFBP-3, insulin-like growth factor binding protein 3.

## Significance | Angiogenesis induced by infection of pathogens

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## 1. Pathogens and Angiogenesis

A pathogen is, broadly speaking, anything that causes a disease in a living organism, and capable of disrupting the normal physiology of said organism. They can be single-celled organisms or large multicellular parasites, infectious agents such as viruses, bacteria, prions, fungi, viroids, or parasitic worms like helminths (D. M. Anderson, Anderson, and Glanze, 2002). Diseases caused by pathogens involve multiple stages, starting from the invasion of the pathogen into the body. Once inside the body, the invading organism may release poisons or toxins which cause damage

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cellular structures of the host organs and tissues. Larger pathogens may also cause physical blockages like disrupting the lymphatic flow or cause obstructions in organs (Wood, 2006). The variety of pathogens and the diverse ways they cause diseases makes it challenging to find new therapeutic agents.

Angiogenesis is a multistep process in which new blood vessels form from pre-existing vessels. It is a vital physiological process in embryo development, wound healing, and in response to ovulation (Adair and Montani, 2010a). Angiogenesis involves the migration and proliferation of endothelial cells, the remodelling of the surrounding extracellular matrix, and the functional maturation the new vessels assembled (Kimura et al., 2000). As the metabolic requirements of the surrounding cells changes, the angiogenic process is either activated or repressed. Although similar, angiogenesis is distinct from vasculogenesis, which is the process by which new blood vessels are formed without pre-existing blood vessels, assembled from the endothelial cell precursor angioblasts and differentiated in situ. Vasculogenesis is responsible for the formation of blood vessels in the developing embryo where there were previously none. After that, angiogenesis is responsible for the growth and expansion of those blood vessels to form a vast complex vascular network (Conway, Collen, and Carmeliet, 2001).

Two types of angiogenesis were identified, namely sprouting angiogenesis and intussusceptive (non-sprouting) angiogenesis (Ribatti, 2006). The two processes involve different cell types and are regulated by different molecules. Sprouting angiogenesis is mainly characterized by local vasodilation, increased vascular

permeability, and cell proliferation (Djonov, Baum, and Burri, 2003). Sprouting angiogenesis starts with vasodilation in response to nitric oxide (NO) during hypoxia, requiring the formation of new blood vessels to satisfy metabolic requirements of the cells in that region. The transcription of vascular endothelial growth factor A (VEGF-A), a signal protein that stimulates angiogenesis, is in part upregulated by NO in most parenchymal cells. VEGF-A mediates an increase in vascular permeability and alterations in cell membrane structure (Kimura et al., 2000). Next, VEGF-A induces the extravasation of plasma proteins to create a temporary support structure which activated endothelial cells would migrate to and form vessel sprouts (Senger, 1996).

Angiopoietin 2 (Ang-2), a glycoprotein, reduces inter-endothelial cell contacts, which detaches the smooth muscle cells and loosens the underlying matrix to allow for the migration of the endothelial cells (Gale and Yancopoulos, 1999). The degradation of the extracellular matrix liberates other growth factors involved in angiogenesis, including basic fibroblast growth factor (bFGF), VEGF, and over 20 matrix metalloproteinases (MMPs). It also exposes the cryptic adhesion sites hidden within the matrix (Conway et al., 2001). The secretion of MMP-2, MMP-3, and MMP-9, and the suppression of tissue inhibitor metalloproteinase-2 (TIMP-2), contributes to vascular sprouting induced by angiopoietin 1 (Ang-1) (Kim et al., 2000). With the matrix removed, the endothelial cells are free to migrate to form new vessels. The migration and the proliferation of the endothelial cells are mediated by various forms of VEGF, angiopoietins, and FGFs.

## Glossary

Pathogen	Type of Pathogen	Diseases Caused	Angiogenic Mediators Activated by Infection
<i>Bartonella henselae</i>	Gram-negative bacterium	Bacillary angiomatosis, bacillary peliosis	NFκB, VEGF, HIF-1, IL-8, ADM, IGFBP-3, CXCR2
<i>Bartonella bacilliformis</i>	Gram-negative bacterium	Oroya fever or Carrion's disease, Peruvian warts	Ang-2, VEGF
<i>Bartonella quintana</i>	Gram-negative bacterium	Trench fever, bacillary angiomatosis, endocarditis	VEGF
<i>Helicobacter pylori</i>	Gram-negative bacterium	Chronic gastritis, gastric ulcers, duodenal ulcers, stomach cancer	IL-8, VEGF, MMP-9
<i>Mycobacterium tuberculosis</i>	Mycobacterium	Tuberculosis	VEGF, IL-8, IL-12, TNFα, MMP-1, MMP-9
Hepatitis B virus (HBV)	Double-stranded DNA virus	Hepatitis B, cirrhosis, hepatocellular carcinoma	HIF-1, HBx, VEGF, Ang-2, MMP-2, MMP-3, MMP-9, MMP-14, COX-2
Hepatitis C virus (HCV)	Single-stranded RNA virus	Hepatitis C, cirrhosis, hepatocellular carcinoma	Ang-2, PIGF, NF-κB, TGF-β, MMP-2, MMP-9, COX-2
Kaposi's sarcoma-associated herpesvirus (KSHV) / human herpesvirus 8 (HHV-8)	Double-stranded DNA virus	Kaposi's sarcoma, primary effusion lymphoma, Castleman's disease	VEGF, Ang-2, TGF-β, IL-6, vIL-6, COX-2
Orf virus	Double-stranded DNA virus	Contagious pustular dermatitis	VEGF-E, MMP-2, MMP-9

### 1.1 Angiogenesis in Health and Diseases

Angiogenesis is a tightly-regulated physiological process resulting from a balance between angiogenic and angiostatic stimuli. In healthy tissues, angiogenesis is stimulated or suppressed according to functional demands (Adair and Montani, 2010b). Unregulated, overexpression of angiogenesis could cause severe tissue dysfunction, and is implicated in the pathogenesis and development of diseases such as rheumatoid arthritis (Paleolog, 2002), diabetic retinopathy (Crawford, Alfaro, Kerrison, and Jablon, 2009), and several chronic inflammatory diseases. In addition, it is also a requirement for the metastasis of tumours. However, insufficient vessel growth or abnormal vessel regression also lead to, or increase the severity of diseases such as cardiac and cerebral ischemia (Krupinski, Kaluza, Kumar, Kumar, and Wang, 1994), hypertension (Struijker, 1998), osteoporosis (Martinez, Esbrit, Rodrigo, Alvarez-Arroyo, and Martinez, 2002) (Yin et al., HIF-1 is composed of the two subunits, HIF-1 $\alpha$  and HIF-1 $\beta$ . HIF-1 $\beta$  is constantly present in mammalian cell nuclei, but the levels of HIF-1 $\alpha$  are affected by changes in the cellular oxygen partial pressure. High levels of HIF-1 $\alpha$  correlates with the overexpression of VEGF and significantly increased microvessel density (Bos et al., 2001). It was also induced by bacterial infection even under normoxia conditions. The expression of HIF-1 $\alpha$  was increased four-fold in wild type mouse macrophages after exposure to Group A Streptococcus under normoxia, which is even more potent than HIF-1 $\alpha$  induction under hypoxia. HIF-1 $\alpha$ -induction under normoxia had also been observed with exposure to methicillin-resistant *S. aureus*, *P. aeruginosa*, and *Salmonella typhimurium* (Peyssonnaud et al., 2005). In infections with human pathogenic Enterobacteriaceae, secretion of bacterial siderophores results in the iron-competition between the bacteria and host cells, resulting in the activation of HIF-1 (Werth et al., 2010). Targeting HIF-1 and the pathways it regulate could potentially provide an alternative treatment to life-threatening infections. Targeting HIF-1 could also be clinically relevant to therapies targeting VEGF or angiogenesis in general (2002), and other disorders.

There are also a number of pathogens that induce angiogenesis during the pathogenesis of the disease they cause. Examples of bacteria capable of causing angiogenesis in its hosts are *Bartonella henselae*, *Bartonella bacilliformis*, *Bartonella quintana*, *Helicobacter pylori*, and *Mycobacterium tuberculosis*. The hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma-associated herpesvirus (KSHV), and orf virus are viruses that induce angiogenesis during infection. With new insights on the angiogenic process and how it contributes to the pathogenicity and intensity of infections, new therapeutic opportunities can be discovered in the future.

### 1.2 Stimulation of Angiogenesis during Infections

In the tissue microenvironment, hypoxia is a characteristic feature during bacterial infection. In an oxygen-deprived environment, mammalian cells activate the highly-conserved transcriptional complex hypoxia-inducible factor (HIF-1). HIF-1 plays an important role in infectious diseases. It enhances the bactericidal capacity of phagocytes and controls the systemic spread of bacteria in mice (Peyssonnaud et al., 2005). HIF-1 binds to the hypoxic response elements (HREs) of target gene regulatory sequences, activating the transcription of genes related to the control of angiogenesis like VEGF (Semenza, 2001) which in turn promotes endothelial cell proliferation and angiogenesis (Forsythe et al., 1996). In addition, HIF-1 stimulates the pro-angiogenic enzyme cyclooxygenase 2 (COX-2), and enhances cell migration by the activation of the matrix metalloproteinases (MMPs) (Vrancken, Paeshuyse, and Liekens, 2012). HIF-1 is activated during *Bartonella henselae* infections, which lead to excessive angiogenesis and the vasculoproliferative disorder bacillary angiomatosis (V. A. Kempf et al., 2005). HIF-1 activation and VEGF mRNA induction has also been observed in HeLa-229 and NHEK cells infected with *Staphylococcus aureus* wild type, *Pseudomonas aeruginosa* ATCC 27853, and *Escherichia coli* ATCC 25922.

## 2. Angiogenesis Induced by Pathogenic Infections

### 2.1 Angiogenesis Induced by Bartonella Infections

#### 2.1.1 Angiogenesis and Bartonella henselae

The gram-negative bacterium *Bartonella henselae* is one of the pathogens capable of inducing angiogenesis in its host, causing the vasculoproliferative disorders bacillary angiomatosis and bacillary peliosis. Bacillary angiomatosis is characterized by the formation of tumour-like lesions in the skin and other organs through the proliferation of blood vessels. Peliosis hepatis is an uncommon vascular condition that primarily affects the liver, characterized by multiple randomly distributed blood-filled cavities throughout it.

Bacteria of the *Bartonella* genus are well-established as bacterial pathogens that causing vasculoproliferative disorders in humans, as they promote endothelial proliferation, matrix invasion, and endothelial tubular differentiation in the hosts (Kirby, 2004). The nature and the severity of the disease manifestation depend on the state of the immune system of the patient. *B. henselae* is normally transmitted by cat scratches or bites, and occasionally through ticks and flies (Haimerl et al., 1999). Infection of the vascular endothelium by this proteobacteria causes tumour-like angiogenic lesions made up by aggregates of immature vascular channels (B. E. Anderson & Neuman, 1997) through a combination of mechanisms including nuclear factor kappa-B (NF $\kappa$ B)-dependent proinflammatory gene activation (Maeno et al., 2002), direct promotion of endothelial cell proliferation (Maeno et al., 1999), inhibition of endothelial cell apoptosis (Kirby and Nekorchuk, 2002), and upregulation of angiogenic growth factors from peripheral cells

and macrophages (Resto-Ruiz et al., 2002).

*B. henselae* expressing pili induces the activation of HIF-1 and the production of vascular endothelial growth factor (VEGF) to stimulate endothelial cell proliferation. Via HIF-1, infected host cells were reprogrammed to secrete VEGF to induce angiogenesis (V. A. Kempf et al., 2001). Pili expression of the bacterium is essential to the triggering of the increased VEGF production. Compared to EA.hy 926 cells infected with bacterial cells that produce pili (Pil+), cells infected with Pil- mutants marked a dramatic decrease in VEGF production (V. A. Kempf et al., 2001). With increased angiogenesis, the bacterium increases its survival by expanding its host cell reservoir as it replicates within the endothelial cells (V. Kempf et al., 2000). The human vascular cell lines EA.hy 926 cells and HeLa cells produce a high amount of VEGF after exposure to *B. henselae*, peaking at 72 hours of co-cultivation. Comparing the RNA microarray of infected and uninfected HeLa cells six hours after infection, genes encoding angioproliferative factors such as VEGF, interleukin-8 (IL-8), adrenomedullin (ADM), and insulin-like growth factor binding protein 3 (IGFBP-3) were up-regulated more than two-fold, with increased protein expression observed for VEGF, IL-8, IGFBP-3, and ADM (V. A. Kempf et al., 2005).

Interleukin-8 (IL-8), a potent promoter of angiogenesis, has been observed to be enhanced in response to *B. henselae* infections (Resto-Ruiz et al., 2002) (Schmid et al., 2004). Unlike most of the other angiogenic factors that are induced by HIF-1, IL-8 is induced by the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) protein complex. *B. henselae* also increases the expression of one of the receptors of IL-8, chemokine (C-X-C motif) receptor 2 (CXCR2). The combined increase of both the IL-8 production and CXCR2 expression indicates that the level of IL-8 signalling is extremely elevated during the infection of *B. henselae* (McCord, Resto-Ruiz, and Anderson, 2006). Increased production of IL-8 was observed in EA.hy 926 cells three days after co-cultivation with *B. henselae* (V. A. Kempf et al., 2001).

### 2.1.2 Angiogenesis and *Bartonella bacilliformis*

Another member of the *Bartonella* genus, *Bartonella bacilliformis*, causes Oroya fever or Carrion's disease, a sickness found only in Peru, Ecuador, and Colombia (Maguina, Garcia, Gotuzzo, Cordero, and Spach, 2001). Infections from *B. bacilliformis* are transmitted through the sandflies in that area (Ihler, 1996). The infection develops into Carrion's disease at the acute phase, characterised by fever, severe haemolytic anaemia, and transient immunosuppression. In the chronic phase, lesions develop due to the proliferation of the endothelial cells, and are known as the Peruvian warts or verruga peruana. After in vitro infection with *B. bacilliformis*, extensive cytoskeletal remodelling of the endothelial cells is observed (Verma, Davis, and Ihler, 2001). It

had been shown that *B. bacilliformis* extracts stimulate endothelial cells-specific proliferation three times of that of the control in vitro and angiogenesis in vivo. The angiogenic factor was thought to be a protein as it was heat sensitive and precipitated with 45% ammonium sulphate (Garcia, Wojta, Broadley, Davidson, and Hoover, 1990). Infection by this bacteria causes the induction of angiopoietin-2 (Ang-2) in vitro and in vivo (Cerimele et al., 2003). Even though Ang-2 promotes cell death and disrupts vascularization, Ang-2 stimulates angiogenesis in the presence of VEGF (Lobov, Brooks, and Lang, 2002).

### 2.1.3 Angiogenesis and *Bartonella quintana*

*Bartonella quintana* is the third member of the *Bartonella* bacteria that causes angiogenesis in its hosts. This bacterium, originally known as *Rochalimaea quintana* and *Rickettsia quintana*, causes trench fever, bacillary angiomatosis, and endocarditis in humans (Ohl and Spach, 2000). Trench fever caused by *B. quintana* was first documented in soldiers during World War I, resulting in the death of one million soldiers in Europe (Jackson & Spach, 1996). These bacteria infect endothelial cells and erythrocytes, causing nuclear atypia, suppression of apoptosis, release of proinflammatory cytokines, and increase of vascular proliferation. Like other bacteria of its genus, *B. quintana* cause the manifestation of bacillary angiomatosis lesions in immunocompromised hosts similar to *B. henselae* (Koehler, Quinn, Berger, LeBoit, and Tappero, 1992). The *B. quintana* strain JK-31, a strain that expresses the variable outer membrane proteins (Vomps) on their surfaces, induced secretion of VEGF from infected human monocyte cell line (THP-1) and HeLa 229 cells (Karem, Paddock, and Regnery, 2000).

### 2.2 Angiogenesis Induced by *Helicobacter pylori* Infections

*Helicobacter pylori*, previously known as *Campylobacter pylori*, is a gram-negative bacterium mainly found in the stomach. It has been linked to the development of chronic gastritis, gastric ulcers, duodenal ulcers, and stomach cancer (Montecucco and Rappuoli, 2001). *H. pylori* induces angiogenesis by up-regulating IL-8, VEGF, angiogenin, and matrix metalloproteinase 9 (MMP-9) genes (Kitadai et al., 2003). Proteases of the MMP family are involved in the degradation of the basement membrane and the extracellular matrix in angiogenesis (Pepper, 2001). Significantly higher cell proliferation and microvessel count have been observed in the tumours of *H. pylori*-positive patients compared to the tumours of patients who received *H. pylori*-eradication therapy (Sasaki et al., 2003). *H. pylori* isolated from gastric cancer patients had been shown to increase the angiogenic activity and cell invasion in the AGS and MKN45 cells (Y.-J. Chang, Wu, Lin, and Chen, 2005). There was an increase in the mRNA expression of angiogenic factors IL-8, VEGF, angiogenin, and ureases urokinase, and MMP-9 in MKN-1 and TMK-1 cells co-cultured with *H. pylori*. An increase of the secretion of IL-8, VEGF, and MMP-9

proteins by the human gastric carcinoma cells was also observed (Kitadai et al., 2003). Urokinase's role in angiogenesis is that it catalyses the conversion from plasminogen to plasmin, which is an enzyme that degrades various extracellular matrix proteins and activates the MMPs and growth factors (Andreasen, Kjoller, Christensen, and Duffy, 1997). Angiogenesis supports the metastasis of the gastric carcinoma cells and therefore promote the spread of the cancer.

### 2.3 Angiogenesis Induced by *Mycobacterium tuberculosis* Infections

Tuberculosis (TB) is a widespread infectious disease caused by *Mycobacterium tuberculosis* and other mycobacteria (Kumar, Abbas, and Aster, 2012). This disease is characterized by symptoms such as chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. The bacteria are spread through microscopic droplets released into the air. TB commonly cause extensive scarring in the upper lobes of the lungs, and is known as extrapulmonary TB if it develops outside of the lungs. However, extrapulmonary TB may coexist with pulmonary TB (Vikram, 1768).

In an ultrastructural analysis of active pulmonary tuberculosis lesions in rats, intense angiogenesis had been observed (Ridley, Heather, Brown, and Willoughby, 1983). The injection of trehalose 6,6'-dimycolate, a cell wall glycolipid of *M. tuberculosis*, into rat corneas successfully induced dose-dependent angiogenesis, with angiogenic mediators VEGF, IL-8, and tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), a cytokine known to increase the secretion of VEGF, found in the lesions at an early stage (Saita, Fujiwara, Yano, Soejima, & Kobayashi, 2000). Clinically, the pro-angiogenic activity of sera from the TB patients was significantly higher than those of the healthy controls. Increased VEGF levels had also been found in the serum (Matsuyama et al., 2000) (Abe et al., 2001), pleural effusion (Kiroopoulos, Kostikas, and Gourgoulanis, 2005), and cerebrospinal fluid of patients with active TB (Matsuyama et al., 2001). The levels of IL-12 and TNF $\alpha$  was also significantly elevated in serum of TB patients when compared to the serum of healthy individuals (Zielonka et al., 2011). When incubated with THP-1 cells, *Mycobacterium tuberculosis* and its major cell antigenic component, lipoarabinomannan (LAM), stimulate the release of MMP-9 and upregulate the expression of genes for MMP-1 and MMP-9 (J. C. Chang et al., 1996). These findings confirmed that TB infections involve the increase of angiogenesis.

### 2.4 Angiogenesis Induced by Hepatitis Virus Infections

#### 2.4.1 Angiogenesis and Hepatitis B Virus (HBV)

The hepatitis B virus (HBV), a member of the Hepadnavirus family, is a blood-borne virus that causes hepatitis B in the liver. It is a partially double-stranded DNA virus of the Hepadnaviridae family. This virus could also cause cirrhosis and hepatocellular carcinoma, and increase the risk of contracting pancreatic cancer (Schwalbe et al., 2008) (M. M. Hassan et al., 2008). Approximately 780 000 persons die each year from hepatitis B infections (Lozano et al., 2013). Acute infections last several weeks and present symptoms that include jaundice, dark urine, extreme fatigue, nausea, vomiting, and abdominal pain. Acute hepatitis could also develop acute liver failure and could eventually lead to death. In chronic liver infections of the virus, cirrhosis of the liver or liver cancer could develop (World Health Organization, 2015). Cirrhosis is a prolonged fibrotic response characterised by the replacement of normal liver tissues by scar tissue, leading to the loss of function of the liver. Cirrhosis is usually accompanied by localized hypoxia, rearrangement of tissue architecture, and angiogenesis. Local hypoxia in the liver tissues stimulates the activation of HIF-1. HBx, a hepatitis B viral protein, increases the protein level in human embryonic kidney (HEK) but not the mRNA level of HIF-1 under both normoxic and hypoxic conditions. This is achieved through direct interaction between HBx and HIF-1 $\alpha$ . HBx also inhibits the binding of the Von Hippel-Lindau tumour suppressor (pVHL) to HIF-1, disrupting the ubiquitin-proteasome pathway that rapidly degrades HIF-1 under normoxia (Moon et al., 2004). The increase in HIF-1 in turn enhances the transcription of VEGF, leading to angiogenesis in the host cells and promote the malignancy of hepatocellular carcinoma (HCC) (Vrancken et al., 2012).

In clinical investigations, the expression rate of VEGF and the mean microvessel density were significantly higher in HBx-positive HCCs than in non-HBV-related HCC tissues (Liu, Hao, Zhao, Niu, & Li, 2010). A significant increase of VEGF mRNA expression was detected in the liver of HBx transgenic mice (Yun et al., 2002). The HBx protein also activates the mitogen-activated protein kinase (MAPK), leading to the increased expression and secretion of Ang-2 in the liver tissues (Sanz-Cameno et al., 2006). Increased levels of Ang-2 promote tumour angiogenesis in the presence of VEGF (Eklund and Saharinen, 2013). Furthermore, HBx had been observed to up-regulate other pro-angiogenic proteins, including MMP-2 (Ou, Tao, Tang, & Yang, 2007) (L.-p. Liu et al., 2010), MMP-3 (Yu, Liu, Lee, Liao, and Shih, 2005), MMP-9 (Chung, Lee, and Kim, 2004), MMP-14 (L.-p. Liu et al., 2010), and COX-2 (Lara-Pezzi et al., 2002) (Cheng et al., 2004). In mice that were subcutaneously injected with Matrigel containing HBx-expressing hepatoma cells, significantly more blood vessels had been observed in the Matrigel compared to those in mice infected with normal hepatoma cells (Lee et al., 2000). It shows that even HBx alone is enough to induce angiogenesis.

**2.4.2 Angiogenesis and Hepatitis C Virus (HCV)**

The hepatitis C virus (HCV) is another virus that infects the liver, even though this virus is unrelated to the HBV. It is an enveloped, positive-sense single-stranded RNA virus of the Flaviviridae fam-

ily. Chronic infections cause scarring in the liver, leading to cirrhosis and may further develop into liver failure, liver cancer, or life-threatening esophageal and gastric varices. Each year, 350 000 to 500 000 people die from hepatitis C-related liver diseases (World Health Organization, 2014).

Liver biopsies of patients with chronic hepatitis showed that increased microvessel density from angiogenesis was more frequent in HCV-positive patients compared to those infected with HBV (Messerini, Novelli, and Comin, 2004). Higher levels of Ang-2 and placental growth factor (PIGF), a member of the VEGF family, were found in the serum of patients with chronic hepatitis C (Mora et al., 2005). The HCV virus is also capable of mimicking hypoxic conditions for HIF-1 $\alpha$  stabilization through its non-structural protein 5A (NS5A), which induces the activation of NF- $\kappa$ B and STAT-3 transcription factors (Gong, Waris, Tanveer, and Siddiqui, 2001). Stabilization of HIF-1 $\alpha$  leads to VEGF activation and up-regulates angiogenesis. The core protein of HCV has also been shown to induce hepatic angiogenesis through the expression of TGF- $\beta$ 2 and VEGF (M. Hassan, Selimovic, Ghozlan, and Abdel-kader, 2009), and the up-regulation of the angiogenic factors MMP-2, MMP-9, and COX-2 (Nunez et al., 2004).

## 2.5 Angiogenesis Induced by Kaposi's Sarcoma-Associated Herpesvirus Infections

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is an endothelial-tropic virus that causes Kaposi's sarcoma lesions in the skin, lungs, and gastrointestinal tract (Safai et al., 1985). The virus' primary site of replication is the oropharynx with shedding found in the saliva (Vieira, O'Hearn, Kimball, Chandran, and Corey, 2001) (Mayama et al., 1998). Kaposi's sarcoma is a cancer common in patients with AIDS (Boshoff & Weiss, 2002), prevalent in the male homosexual population, and can manifest as an advanced disseminated cancer with increased morbidity and mortality (Gallo, 1998). It also causes primary effusion lymphoma (Cesarman, Chang, Moore, Said, and Knowles, 1995) and some types of Castleman's disease. Early lesions are characterized by an inflammatory-granulation type reaction with activated proliferating endothelial cells, forming abnormal new blood vessels and infiltrated by leukocytes producing VEGF (Ruszczak, da Silva, and Orfanos, 1987) (Sakakibara, Pise-Masison, Brady, and Tosato, 2009). The lesions produced are similar to lesions produced from infections of *B. henselae*, characterized by proliferating spindle-shaped endothelial cells, neo-vascular structures, inflammatory cells, and an abundance of inflammatory cytokines, growth factors, invasive factors, and angiogenic factors including VEGF (Cornali et al., 1996), Ang2 (Vart et al., 2007), angiogenins (Sadagopan et al., 2009), transforming growth factor  $\beta$  (TGF- $\beta$ ) (Di Bartolo et al., 2008), and interleukin-6 (IL-6).

Viral interleukin-6 (vIL-6) is a multifunctional cytokine encoded by KSHV and expressed in KSHV-infected cells that had switched from latency to the viral replication stage (Dawes, Lapidus, Berlin, and Meyer, 1990). It is structurally homologous to human IL-6, exhibiting 24.7% amino acid similarity to IL-6 and conserving sequences involved in receptor binding (Neipel et al., 1997). IL-6 is a critical regulator of cell growth and differentiation, and like IL-6, vIL-6 is capable of promoting angiogenesis in humans by indirectly triggering VEGF expression through VEGF mRNA induction (Cohen, Nahari, Cerem, Neufeld, and Levi, 1996). Murine fibroblast NIH3T3 cells transformed to produce vIL-6 gave rise to tumour tissues that were highly vascularised and expressed high levels of VEGF, increasing the blood supply to the tumours. Cytoplasmic and membrane VEGF was also detected in cells from tumours, spleens, and lymph nodes of mice inoculated with vIL-6-expressing cells (Aoki et al., 1999). Tissues that were KSHV-positive for Castleman's disease had marked vIL-6 expression, sometimes in conjunction with cellular IL-6 (Parravinci et al., 1997). The lymphoid hyperplasia associated with this disease is attributed with excessive vascularization in the germinal centres from VEGF expression of non-lymphoid cells (Foss et al., 1997). KSHV is also capable of regulating host gene expression. COX-2, a pro-angiogenic and anti-apoptotic enzyme, is highly induced upon de novo infection of human microvascular endothelial cells (HMVEC-d) and human foreskin fibroblast (HFF) cells (Shelby et al., 2007). Abundant COX-2 expression was detected in KS skin tissue and KS lymph node sections. Strong COX-2 staining was observed in the eye orbit, tonsil and mouth, and the small bowel of the patients' tissue samples (Sharma-Walia et al., 2010). It is believed that KSHV infections induce an angiogenic, GFs-, and MMPs- rich microenvironment and a strong cytokine network that is conducive to the continued proliferation and migration of KSHV (Dupin et al., 1999) (Qian, Xie, Ye, and Gao, 2007).

## 2.6 Angiogenesis Induced by Orf Virus Infections

The orf virus is a parapox virus that primarily infects sheep and goats, causing contagious pustular dermatitis or contagious ecthyma. It could also infect humans through direct contact with infected sheep and goats, fomites carrying the virus, or contact with infected carcasses and non-living materials. It is therefore an occupational hazard for shepherds, veterinarians, butchers, and shearers. The virus causes a local purulent-looking papule at the infection site that spontaneously resolves after persisting 7 to 10 weeks, with massive capillary proliferation and dilation (Groves, Wilson-Jones, and MacDonald, 1991). While infections by the orf virus in humans usually resolve spontaneously without specific treatment after 4-8 weeks, they could still be life-threatening in the immune-compromised.

The lesions caused by the orf virus are pyogenic granuloma-like lesions, histopathologically characterised by massive capillary

proliferation and dilation. In the case of an 8-year old female with thermal burns infected with the orf virus, histopathological examination revealed massive capillary proliferation in the lesions (Biyik Ozkaya et al., 2014). The orf virus encodes VEGF-E, a member of the VEGF family with high sequence similarity to VEGF-A121 (Lyttle, Fraser, Fleming, Mercer, and Robinson, 1994). VEGF-E carries the characteristic cysteine knot motif found in all mammalian VEGFs, and has similar bioreactivities with VEGF-A. Its angiogenic activity was just as potent as VEGF-A. Just like VEGF-A, VEGF-E induces tissue-factor (TF) expression, the proliferation of vascular endothelial cells, and stimulates angiogenesis in vivo in the avascular rabbit cornea of albino rabbits. (Meyer et al., 1999). The angiogenic activity of VEGF-A has been attributed to its binding to the high-affinity receptors VEGFR-1 (Klagsbrun and D'Amore, 1996) and VEGFR-2 (Holmes, Roberts, Thomas, and Cross, 2007). VEGF-E does not bind to VEGFR-1, but is a high affinity ligand for VEGFR-2. The activation of VEGFR-2 alone is sufficient to effectively stimulate angiogenesis. (Meyer et al., 1999).

Injection of VEGF-E into normal mouse skin in the absence of infection increased the number of endothelial cells and blood vessels in the dermis, while qualitative RT-PCR showed that VEGF-E increase MMP-2 and MMP-9 expression (Wise et al., 2012). Infections of recombinant orf viruses with their viral VEGF gene disabled resulted in reduced vascular permeability induction, VEGFR-2 activation, and vascular endothelial cell mitogenesis. Hence lesions from the infection of recombinant orf had significantly less blood vessel proliferation, even though virus growth in tissue cultures were not affected (Savory, Stacker, Fleming, Niven, and Mercer, 2000) (Meyer et al., 1999).

### 3. Conclusion

In this review, pathogenic infections that could lead to excessive and abnormal angiogenesis were discussed. With increased understanding of how pathogens induce angiogenesis in diseases, early detection processes may be derived through the detection of angiogenic factors as markers. Novel treatment strategies for those diseases may be found through anti-angiogenesis therapies. Anti-angiogenesis drugs developed for the treatment of cancer could also be used for the treatment of these pathogenic diseases. Targeting angiogenesis is also a good way to control the development of those diseases if the pathogen involved is drug-resistant and cannot be cured by the common antibiotics.

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#### Author Contribution

Brownyn L. made substantial contributions to the conception and design of the manuscript, review of the literature, and drafting of the manuscript and figures. A. M. S. Abdul Majid and A. S. Abdul Majid supervised every step in the design, structure and preparation of the manuscript and gave the final approval of the version to be published. All authors read and approved the final manuscript.

#### Competing financial interests

The author(s) declare no competing financial interests.

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