Infections and cardiovascular disease: is \textit{Bartonella henselae} contributing to this matter?

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Cardiovascular disease is still the major cause of death worldwide despite the remarkable progress in its prevention and treatment. Endothelial progenitor cells (EPCs) have recently emerged as key players of vascular repair and regenerative medicine applied to cardiovascular disease. A large amount of effort has been put into discovering the factors that could aid or impair the number and function of EPCs, and also into characterizing these cells at the molecular level in order to facilitate their therapeutic applications in vascular disease. Interestingly, the major cardiovascular risk factors have been associated with reduced number and function of EPCs. The bacterial contribution to cardiovascular disease represents a long-standing controversy. The discovery that \textit{Bartonella henselae} can infect and damage EPCs revitalizes the enduring debate about the microbiological contribution to atherosclerosis, thus allowing the hypothesis that this infection could impair the cardiovascular regenerative potential and increase the risk for cardiovascular disease. In this review, we summarize the rationale suggesting that \textit{Bartonella henselae} could favour atherogenesis by infecting and damaging EPCs, thus reducing their vascular repair potential. These mechanisms suggest a novel link between communicable and non-communicable human diseases, and put forward the possibility that \textit{Bartonella henselae} could enhance the susceptibility and worsen the prognosis in cardiovascular disease.

Introduction

Cardiovascular disease (CVD) is the primary cause of death all around the world and in 2008 accounted for 30\% of all-cause mortality (World Health Organization, 2011). CVD, and, more precisely atherosclerotic CVD, is predicted to remain the single leading cause of death (23.3 million deaths by 2030) (Mathers & Loncar, 2006). Despite the fact that major risk factors for CVD have been firmly established, a quarter of people presenting the disease do not show any of the known cardiovascular risk factors (Magnus & Beaglehole, 2001). Therefore, there is considerable interest in looking for novel components affecting cardiovascular health, especially for those that could improve global cardiovascular risk prediction. In fact, the lipid hypothesis, which recognizes elevated plasma levels of low-density lipoprotein cholesterol as the primary cause of atherosclerosis and consequent CVD, is evolving and in the last couple of decades a large credit has been given to the potential role of inflammation in atherogenesis (Ross, 1999).

Abbreviations: Ang-1, angiopoietin-1; BA, bacillary angiomatosis; BCNE, blood-culture-negative endocarditis; BP, bacillary peliosis; CVD, cardiovascular disease; EC, endothelial cell; EPC, endothelial progenitor cell; HSC, haematopoietic stem cell; IE, infectious endocarditis; MI, myocardial infarction; T4SS, type IV secretion system; VEGF, vascular endothelial growth factor.
Based upon the immuno-inflammatory response elicited by infectious disease, the microbiological contribution to atherosclerosis, the pathological basis of the vast majority of CVD, represents a long-standing controversy (Nieto, 2002; Rosenfeld & Campbell, 2011). An abundance of data suggest that several infectious agents, such as *Chlamydothihila pneumoniae*, *Helicobacter pylori*, cytomegalovirus and periodontal pathogens, might contribute to atherosclerotic vascular diseases (Chatzidimitriou et al., 2012). However, although lowering plasma cholesterol reduces overall and cardiovascular mortality (Steinberg, 2006), antibiotic treatments failed to do so (Cannon et al., 2005; Grayston et al., 2005; O’Connor et al., 2003). Nevertheless, the finding that the bacterium *Bartonella henselae* can infect endothelial progenitor cells (EPCs) (Salvatore et al., 2008) suggests an alternative mechanism for infectious diseases to promote atherosclerotic CVD. Indeed, *Bartonella henselae*-infected EPCs could reduce the endothelial repair and replacement potential with the subsequent enhancement of vascular inflammation and degeneration. Therefore, this recent evidence could relate infective agents, regenerative medicine and CVD.

Regenerative medicine aims at restoring the original structure and function of damaged tissues by using tissue-specific progenitor cells and avoiding fibrosis and scar formation. The societal burden imposed by CVD could particularly benefit from regenerative medicine, which might help both in preventing and curing the disease.

Presently, it is prudent to indicate vascular maintenance and repair as the most likely possibility to counteract the onset and development of CVD, while *de novo* vascularization of ischaemic tissue remains still a distant chimera.

The aim of this review is to investigate the possibility that some types of infection, by modifying the susceptibility to and/or the course of CVD, could represent novel risk or prognostic factors of CVD.

**Infectious disease and CVD**

The pathological evidence of inflammatory changes within the arterial wall has prompted scientists to recognize the infectious component of atherosclerotic CVD for the past 150 years (Mayerl, 2006). Indeed, accumulation of macrophages and activated T-lymphocytes, cytokine production and consequent increase of the expression of adhesion molecules on the surface of the overlaying dysfunctional endothelium are all characteristics that were identified in the atherosclerotic plaque (Ross, 1999). The lipid-induced transformation of macrophages into foam cells, the proliferation of smooth muscle cell and the production of matrix metalloproteinases (MMPs) are also crucial events in the evolution of the plaque. In particular, MMPs produce fissuring of the arterial wall by breaking down intramural deposits of collagen and elastin; this, in turn, causes the adherence of platelets and activation of the coagulation cascade at the lesion site leading to thrombosis, major occlusion of the atherosclerotic vessel, and consequent myocardial infarction or cerebrovascular accident (Libby et al., 2009). This novel basic knowledge has translated into clinical application: indeed, enhancement of the assessment of cardiovascular risk was obtained by also taking into account the plasma level of C-reactive protein (CRP), a general inflammatory marker secreted by the liver in response to IL-6 stimulation (Ridker et al., 2008).

The inflammatory hallmarks of atherosclerosis have driven many researchers to study the hypothesis that microbial infections could cause, accelerate or aggravate the atherosclerotic CVD.

About four decades ago, virus-induced cholesterol crystals were observed in cultured cells, and such crystals are known to form when cholesterol accumulates in the plaque and to activate inflammasomes (Fabricant et al., 1973; Duewell et al., 2010). Moreover viral infection was shown to induce experimental atherosclerosis and also to alter aortic cholesterol metabolism and accumulation (Fabricant et al., 1978; Hajjar et al., 1986).

Interestingly, repeated inoculations of *Chlamydothihila pneumoniae* increased lipid accumulation in the aortic sinus of normocholesterolemic mice (Tôrömångas et al., 2005). A number of epidemiological studies have demonstrated an association between infections with *Chlamydothihila pneumoniae*, cytomegalovirus and *H. pylori*, and the presence of coronary and carotid atherosclerosis (Ameriso et al., 2001; Franceschi et al., 2002; Grayston, 2000; He et al., 2014; Mayr et al., 2000; Melnick et al., 1993). Very impressive data were obtained in a large longitudinal study on 572 patients with atherosclerosis; in this setting, the authors showed that the extent of the atherosclerotic disease was associated with elevated IgA and IgG titres to infectious agents and CVD mortality was increased by the number of infectious pathogens (Espinola-Klein et al., 2002). Another large human study, involving 657 subjects with no history of CVD demonstrated that the mean carotid intima-media thickness was related to the magnitude of the periodontal bacterial infection (Desvarieux et al., 2005).

Indeed, raised serum titres of antibody to *Chlamydia* were observed in patients with acute myocardial infarction or chronic coronary heart disease (Saikku et al., 1988). In addition, elevated concentrations of lipopolysaccharides (also known as endotoxins, the large molecules of the outer wall of Gram-negative bacteria) have been considered a risk factor for experimental and, possibly, human atherosclerosis (Prasad et al., 2002). Among other findings suggesting an association between infectious agents and atherosclerosis, bacterial DNA has been detected in atheromatous plaques by quantitative PCR (Kozarov et al., 2006; Ott et al., 2006). Very recently, 16S RNA sequencing detected 17 identical phylotypes in atherosclerotic plaques and subgingival samples from CVD patients suggesting bacterial transfer between periodontal pockets and coronar...
(Serra e Silva Filho et al., 2014). In addition, some bacterial strains were also isolated and cultivated from atheromas (Fiehn et al., 2005; Kozarov et al., 2005).

It is also worth mentioning that an antimicrobial activity has been attributed to statins, the most powerful drugs for lowering plasma cholesterol and cardiovascular mortality (Falgas et al., 2008; Sun & Singh, 2009). These data indirectly lend support to the infective hypothesis of CVD, implying that reduction of cardiovascular mortality following statin treatment could be due, at least in part, to the statin antimicrobial effect (Kozarov et al., 2014).

As far as cellular and molecular mechanisms that could mediate the pro-atherogenic activity of infectious agents, the development of the atherosclerotic plaque could be favoured by the infection-associated chronic inflammation of the vessel wall and endothelial dysfunction (Ridker, 2002; Epstein et al., 2009). Indeed, bacteria seem to activate the most relevant cell types in atherosclerotic plaque development: leukocytes, endothelial cells (ECs) and smooth muscle cells. Furthermore, bacteria stimulate toll-like receptor-mediated cytokine release in leukocytes, the expression of adhesion molecules in ECs, and a prothrombotic response in smooth muscle cells (Kozarov, 2012; Roth et al., 2009; Stassen et al., 2008). This evidence was further supported by transcriptomic analysis of human aortic endothelial cells (HAECs) after infection with Porphyromonas gingivalis (Chou et al., 2005). In addition, P. gingivalis has also been shown to induce apoptosis in HAECs and the secreted proteins of the same bacterium to disrupt and alter trans-endothelial resistance in polarized ECs (Kozarov et al., 2003; Roth et al., 2007).

**The role of endothelial progenitor cells in vascular integrity**

A plethora of endothelium-related cells have been attributed the capacity to replace damaged endothelium (Table 1). Firstly, intact mature ECs, adjacent to injured intima, were considered one of the major components of the repair process (Carmeliet, 2000). Also circulating ECs (mature ECs that may have detached from the vascular intimal layer following some injury and increased in number in the presence of vessel damage) have been ascribed some kind of reendothelialization capability (Duda et al., 2007; Moroni et al., 2005; Yoder, 2010). However, besides these mature ECs, with very limited proliferative capacity, a major step forward was taken when it was observed that a subtype of peripheral blood mononuclear cell, expressing surface markers of both haematopoietic stem cells and primary embryonic hemangioblasts (CD34 and VEGFR2), was able to differentiate into ECs and home at ischaemic angiogenic sites (Asahara et al., 1997). Later on, CD34+ cells with similar capabilities were isolated from the bone marrow and were termed EPCs (Shi et al., 1998), but the group of Rafii suggested that true EPCs should coexpress

<table>
<thead>
<tr>
<th>Cell name</th>
<th>Molecular phenotype</th>
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<tr>
<td>c.f.u.-EC</td>
<td>CD31, CD105, KDR, vWF, Ac-LDL, CD14, CD45, CD115</td>
<td>Yoder et al. (2007)</td>
</tr>
<tr>
<td>ECFC</td>
<td>CD31, CD105, CD144, CD146, KDR, vWF, UEA-1, Ac-LDL</td>
<td>Yoder et al. (2007)</td>
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<td>VEC</td>
<td>CD34, Flt1, KDR</td>
<td>George et al. (2011)</td>
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<td>Myelo/monocytic progenitors</td>
<td>Flt1, KDR</td>
<td>George et al. (2011)</td>
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<td>MEC</td>
<td>VE-Cadherin</td>
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<td>MC</td>
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<td>MAPC</td>
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<td>LEC</td>
<td>KDR</td>
<td>George et al. (2011)</td>
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<td>Hemangioblast</td>
<td>KDR, CD34</td>
<td>George et al. (2011)</td>
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<td>HC</td>
<td>CD133</td>
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<td>EPC</td>
<td>CD133, KDR</td>
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<td>EC</td>
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<td>CHS</td>
<td>CD45</td>
<td>George et al. (2011)</td>
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<td>Early EPC</td>
<td>CD34, CD133, VEGFR2, CD14, CD45, vWF, CD31</td>
<td>Sen et al. (2011)</td>
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<td>Late outgrowth EPC</td>
<td>vWF, VEGFR2, CD31, CD45, CD144, CD34</td>
<td>Sen et al. (2011)</td>
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<tr>
<td>Mature EC</td>
<td>vWF, VEGFR2, CD31, CD144, CD34</td>
<td>Sen et al. (2011)</td>
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<tr>
<td>CEC</td>
<td>CD31, CD34, CD105, CD144, CD146, CD202b, VEGFR2</td>
<td>Yoder (2010)</td>
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<td>CAC</td>
<td>CD133, VEGFR2, CD115, CD31, UEA-1, e-NOS, vWF, ac-LDL, ALDH</td>
<td>Hirschi et al. (2008)</td>
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<tr>
<td>ECFC</td>
<td>CD34, VEGFR2, CD31, UEA-1, e-NOS, vWF, ac-LDL</td>
<td>Hirschi et al. (2008)</td>
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CAC, circulating angiogenic cell; CEC, circulating endothelial cell; c.f.u.-EC, colony forming unit endothelial cell; c.f.u.-Hill, colony forming unit-Hill; CHS, cells of haematopoietic system; ECFC, endothelial colony forming cell; HC, haematopoietic cell; LEC, lymphatic endothelial cell; MAPC, multipotent adult progenitor cell; MC, megakaryocytes; MEC, mature endothelial cell; VEC, vascular endothelial cell.
CD133, a recognized marker of pluripotent cells (Mahmood et al., 2011; Peichev et al., 2000). Interestingly, further studies associated the presence/absence of surface markers with specific functionalities of EPCs, like vascular homing and repair competence, incorporation into the damaged endothelium, and in vivo vessel formation (Asahara et al., 1997; Becher et al., 2010; Friedrick et al., 2006; Hur et al., 2004; Sievking et al., 2008).

EPCs are being increasingly recognized as key players in the maintenance of endothelial integrity, injury repair and postnatal neovascularization (Asahara et al., 2011; Hirschi et al., 2008; Napoli et al., 2008; Sen et al., 2011; Yoder et al., 2007). An indirect contribution of EPCs to neovascularization has been proposed, namely a paracrine effect of EPCs, due to the secretion of pro-angiogenic cytokines and growth factors that induce proliferation and migration of pre-existing ECs (Asahara et al., 2011). Indeed, it has been demonstrated that EPCs migrate to sites of vascular injury and secrete vascular endothelial growth factor (VEGF), hepatic growth factor, angiopeitoin-1 (Ang-1) and many more vasculogenic factors (Miyamoto et al., 2007). These observations emphasized that these cells could allow therapeutic vasculogenesis in ischaemic tissues. Moreover, ex vivo isolated EPCs improved blood flow and tissue function in animal models of myocardial infarction (MI) and hind limb ischaemia (de Nigris et al., 2005; Kawamoto et al., 2003; Urbich et al., 2003). More importantly, several clinical studies indicate the possibility of using EPCs as therapeutic strategies for myocardial neovascularization and endothelial regeneration (Hristov & Weber, 2006; Shantsila et al., 2008; Vanderheyden et al., 2007). Recent studies also suggest the possibility of using new stents to attract EPCs. The EPC-capturing technology has been shown to promote the arterial healing response by binding circulating EPCs, resulting in the rapid establishment of a functional endothelial monolayer (Aoki et al., 2005; Barsotti et al., 2009).

Several other studies have shown that bone marrow-derived progenitor cells significantly improve blood supply in patients with peripheral artery disease and MI (Assmus et al., 2002; Casamassimi et al., 2012; Tateishi-Yuyama et al., 2002). However, further human studies, aimed at evaluating the therapeutic efficacy of EPC infusion, gave contradictory results with significant improvement of limb ischaemia, but only very modest benefits of left ventricular function after MI (Lasala & Minguell, 2009; Martin-Rendon et al., 2008; Schächinger et al., 2004). In this regard, differences in the route of administration of the progenitor cells could contribute to conflicting evidence. Indeed, either intramuscular or intra-arterial administration of progenitor cells have been used to treat peripheral artery disease, while intra-coronary injection has been used to treat MI.

**Bartonella henselae: mechanisms of infection and cardiovascular localization**

*Bartonella henselae*, a facultatively intracellular Gram-negative bacterium, causes cat-scratch disease, a benign infection often characterized by lymphadenopathy or by an asymptomatic course in immunocompetent patients. However, *Bartonella henselae* infections occur more frequently and cause poorer-prognosis diseases in immunocompromised patients (Fig. 1) (Maguïna et al., 2009; Picascia et al., 2015). In these patients, *Bartonella henselae* can develop bacillary angiomatosis (BA) or peliosis (BP), vasoproliferative tumour lesions of the skin or the inner organs, respectively (Mosepele et al., 2012; Relman et al., 1990), which derive from bacterial colonization and activation of human ECs inducing bacteraemia and fever of unknown cause (Chomel et al., 2009). In addition, *Bartonella henselae*, as also *Bartonella quintana*, causes blood-culture-negative endocarditis (BCNE), as indicated by its isolation from native aortic valve tissue of people affected by infectious endocarditis (IE) (Fournier et al., 2001; González et al., 2014; Katsoulis & Massad, 2013; Lamas et al., 2013; Que & Moreillon, 2011). Furthermore, because of the negativity of the blood culture, the diagnosis of BCNE is usually considerably delayed; this could be the reason why most patients present acute cardiac failure, cardiac murmurs, dyspnoea and bibasilar rales, thus suggesting global cardiac failure (Brouqui & Raoult, 2001; Dimopoulos et al., 2012). Therefore, the possibility of *Bartonella* spp. infection must be considered in every patient with IE.

In the mammalian reservoir, *Bartonella henselae* initially infects a yet unrecognized primary niche, which disseminates micro-organisms into the bloodstream leading to the establishment of a long-lasting intraerythrocytic bacteremia (Chomel et al., 2009). Recently, a murine model of chronic infection in immunocompromised SCID/Beige mice showed the ability of bacteria to recapitulate human pathologies. Indeed, in this model, bacteria grow in extracellular aggregates, embedded within collagen matrix, similar to the observations in BP, BA and cat-scratch disease (Chiaraviglio et al., 2010). Bacterial VirB type IV secretion systems (T4SSs) represent crucial pathogenic factors that have contributed to the *Bartonella henselae* expansion in nature; in fact, T4SSs facilitate adaptation to mammalian hosts (Schmid et al., 2004; Schülein et al., 2001) by translocation of a cocktail of Bartonella effector proteins (Beps) into host cells (Okujava et al., 2014). The ability to survive in these cells helps *Bartonella henselae* to escape the host immune response, with its low-endotoxic-potency lipopolysaccharide (Zähringer et al., 2004). Until now, cellular immune response was considered the only hallmark of immunity to intracellular pathogens. Even so, the mechanisms underlying *Bartonella henselae* evasion of the human immune system response are still not fully understood (Mosepele et al., 2012). Invasive bacterial pathogens, during the infection, exploit various cellular processes to facilitate their uptake into an intracellular compartment of the host cells. The
endocardium is one of the most severe localizations of Bartonella infection and is an optimal point to transfer the microbe to blood cells.

The interactions between human pathogenic bacteria and human vascular progenitor cells is a matter of increasing attention and many lines of research aim to clarify how infective events can contribute to worsening vascular pathologies.

**Endothelial cells and Bartonella henselae**

It is known that erythrocytes and ECs are target cells of Bartonella infection (Dehio, 2001) and the location within these cells is also believed to protect Bartonella spp. from antimicrobial agents (Rolain et al., 2001, 2003). Intraerythrocytic and endothelial/periendothelial persistence of Bartonella are distinguishing features in immunocompetent and immunocompromised hosts, respectively (Mosepele et al., 2012).

Mechanisms required to infect human erythrocytes and ECs are (i) massive rearrangements of actin cytoskeleton with formation of bacterial aggregates (invasome) (Dehio, 2001); (ii) NFκB-dependent proinflammatory activation, leading to adhesion molecule expression and chemokine secretion (Kempf et al., 2001; Resto-Ruiz et al., 2002); (iii) inhibition of apoptosis (Kirby & Nekorchuk, 2002); (iv) two T4SSs (Trw and VirB) to adapt to a wide range of mammalian hosts, both essential for the interaction with the host but at different stages of the infection cycle (Okujava et al., 2014).

Inhibition of apoptosis, together with induction of cell proliferation, are pivotal mechanisms allowing Bartonella permanence into the host cell. Indeed, Bartonella directly induces EC proliferation and inhibits human umbilical vein endothelial cell apoptosis, thus suggesting a direct and indirect role of the pathogen in vasoproliferation (Kirby & Nekorchuk, 2002; Pulliainen & Dehio, 2009; Schmid et al., 2004). Bartonella henselae-triggered vasculo-proliferative lesions resemble tumour angiogenesis, the pathological process of new capillary formation out of pre-existing blood vessels (Varanat et al., 2013). Components of the VEGF family are essential regulators of neo-angiogenesis under physiological as well as pathological conditions (Takahashi & Shibuya, 2005). VEGF is secreted from Bartonella henselae-infected macrophages.
Although several studies have highlighted the main pathogenic mechanisms of *Bartonella henselae* infection (Dehio, 2008; Okujava et al., 2014; Schülein et al., 2001), to date it is still unclear what is the primary niche of the bacterium *in vivo*. Three loci have been proposed as the primary sites of infection: extracellular matrix, bone-marrow stem cells, and mature ECs (Mosepele et al., 2012). Additionally, based on the involvement of lymph nodes in the progression of bartonellosis, a role for the migratory cells of the lymphatic system (lymphocytes or mononuclear phagocytes) in the establishment of the primary niche of *Bartonella* infection has been proposed (Harms & Dehio, 2012). As previously mentioned, Salvatore et al. (2008) demonstrated that isolated EPCs internalize *Bartonella henselae*, probably constituting an additional circulating niche of this pathogen. Mobilized EPCs could carry the pathogen to other organs and, more importantly, to the endothelium of the microcirculation.

On this basis, it is plausible that the colonization of ECs and EPCs by *Bartonella* could profoundly alter the

![Fig. 2. A proposed mechanism to explain the reduced vascular repair potential in people infected by *Bartonella henselae*. A low level of cardiovascular risk factors can induce minimal endothelial injury; the intracellular bacterium reduces the number and function of EPCs that can efficiently fix the damaged endothelium, thus favouring the development of the atherosclerotic plaque. LDL, low density lipoprotein](image-url)
maintenance of vascular homeostasis, either by impairing the potential of these cells to regenerate the endothelial layer (Fig. 2) or by promoting the development of vasoproliferative tumours. In fact, it has been reported that *Bartonella henselae* could reduce the function of EPCs (Salvatore et al., 2008), induce the hyper-proliferation of ECs *in vitro*, and be associated with tumours of the vascular system in patients (Kaiser et al., 2011; Koehler et al., 1997; Leong et al., 1992; Pulliainen & Dehio, 2009).

**Conclusion**

CVD remains a major burden on public health all over the world, and, therefore, the scientific and societal interest in the field is still very strong.

Infectious agents can be detrimental to the cardiovascular apparatus through different mechanisms such as direct microbial invasion of the vascular cells. This ability allows the microbes to escape the cellular/humoral immune response, to survive in an intracellular environment, and to avoid the lysis that can induce the chronicity of the vascular inflammations. In addition, bacteria can cause endothelial activation/dysfunction and the secretion of inflammatory cytokines with stimulation and migration of leukocytes, thus promoting atherogenesis. However, infectious diseases can be detrimental to cardiovascular health not only because they directly promote atherogenesis, but also because they could indirectly contribute to atherosclerosis by reducing the endothelial repair potential of adult stem cells. To address this point we use as a paradigm the recent finding that *Bartonella henselae* is able to infect EPCs and reduce their number and functionality (Salvatore et al., 2008). Since circulating EPCs play an important role in accelerating endothelization at sites of vascular damage, it is conceivable to hypothesize that the atherosclerotic plaque growth is enhanced and plaque stability is reduced by a spoilt asset of endothelial precursors.

The evidence summarized herein lends support to the possibility that *Bartonella henselae* infection could represent a novel risk and/or prognostic factor for CVD. Further studies are needed in order to support the involvement of *Bartonella*-endothelial interaction in the onset and evolution of CVD.

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Bartonella henselae and cardiovascular disease