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The many faces of bacterium-endothelium interactions during systemic infections

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Abstract

A wide variety of pathogens reach the blood circulation during viral, parasitic, fungal or bacterial infections, causing clinically diverse pathologies. Such systemic infections are usually particularly severe and frequently life-threatening despite intensive care, in particular at the age of antibiotic resistance. Because of its position at the interface between the blood and the rest of the organism, the endothelium plays a central role during these infections. Through several examples of systemic infections, we propose to explore the diversity of interactions between pathogens and the endothelium. These examples reveal that bacterial pathogens target specific vascular beds and affect most aspects of endothelial cell biology ranging from cellular junction stability to endothelial cell proliferation or inflammation.

THE ENDOTHELIUM AS A SITE OF BACTERIAL INFECTIONS

The endothelium refers to the layer of endothelial cells (ECs) lining the inner surface of blood vessels that span the entire body and ensure the distribution of blood throughout the organism (1). It can be estimated that the human body contains the staggering number of 100 000 km of blood vessels, more than twice the earth's circumference (2). Therefore, a bacterium reaching the circulation is engaged in a maze of huge proportion. Moreover, a pathogen travelling throughout the circulation does not encounter a homogeneous environment, as an important feature of the vascular network is its diversity. Although endothelial cells are present in all vessels, the organization of the vessel wall – formed by three layers referred to as the *tunica intima*, *media* and *adventia* (from the vessel lumen outward) – is different among different vessel types and different organs (3). Vessels can be first differentiated by the complex extracellular matrix layers surrounding them. For instance, elastic arteries such as the aorta are surrounded by 50 elastic layers providing them unique mechanical properties (3). Second, the cellular content is also different according to vessel type, the wall of arteries and veins contains a layer of smooth muscle cells (SMCs) that provides their capacity to relax or constrict in response to vasoactive molecules (4). An additional level of complexity in the network stems from the fact that larger vessels, veins or arteries are themselves vascularized by smaller vessels, the *vasa vasorum* (5). Although endothelial cells are constituent of all vessels, they themselves present different properties depending on their anatomical location, in particular in the case of capillaries. The lumen of *continuous capillaries,* which are the most common, are lined with an uninterrupted layer of endothelial cells. *Fenestrated capillaries*, typically present in glomeruli of the kidney, are laced with 50-80 nm openings thus changing their permeability properties. In the liver, *sinusoidal*

capillaries contain numerous holes that can reach several microns in diameter and could in principle allow objects such as bacteria to escape the circulation (6). Also, particularly relevant to infection, sinusoidal capillaries host a large number of Küpffer cells, phagocytic cells that constantly filter the blood from particulate matter including bacteria (7). Finally, the heart, a central element of the circulation network and also a potential site of infection, displays a specialized endothelium referred to as the *endocardium*. In contrast to the endothelium, the endocardium is constituted of three juxtaposed layers that ensure *i)* its physical anchorage to the surface of the myocardium (the heart muscle), *ii)* its mechano-elastic properties allowing its adaptation to the heart contraction and relaxation cycles and *iii)* its low permeability thanks to a sealed monolayer of endothelial cells (8).

Although usually viewed as a static structure, the design of the blood vessel network is dynamic, in particular in the case of the smaller vessels, first during development but also following wound healing, cancer development, ischemia or infection (9, 10). During development, *vasculogenesis* supports the establishment of the arteries and the veins that transport the blood from and back to the heart, respectively (11). An additional mechanism, referred to as *angiogenesis*, gives rise to smaller vessels, such as blood capillaries of few micrometers in diameter, which deliver oxygen and nutrients to the body's tissues. These vessels elongate from endothelial sprouts emanating from pre-existing vessels and invade non-vascularized areas (12). Of note, capillaries are also able to interconnect through anastomosis, a process resulting in the fusion of two capillary growing-ends (13). Therefore, pathogens reaching the circulation encounter a complex, diverse and dynamic network.

CELLULAR JUNCTIONS AS THE GATEKEEPERS OF THE ENDOTHELIAL BARRIER

Through the fine control of vessel permeability, intercellular junctions within the endothelium are at the heart of the maintenance of vascular integrity, thus ensuring the proper barrier function of the endothelium (14). Among the two main types of endothelial cell-cell junctions, *adherens* junctions (AJ) are ubiquitously found, whereas tight junctions (TJ) are mainly located in endothelial barriers with a very high selectivity (15). This is the case of the blood-brain barrier, where tight junctions ensure the charge- and size-selective exchanges between the cerebral vasculature and the central nervous system (CNS) (16), thus participating in the protection of the brain parenchyma from bacterial invasion, for instance. The main component of *adherens* junctions is the intercellular adhesion molecule Vascular Endothelial (VE)-Cadherin. VE-Cadherin proteins expressed at the surface of neighboring endothelial cells engage their extracellular domain within homotypic interactions that are stabilized by extracellular calcium (17), thus ensuring the sealing of the endothelium. Platelet-Endothelial Cell Adhesion Molecule (PECAM)-1 also participate in the structural integrity of AJs (18). Intracellularly, VE-Cadherin is linked to the actin cytoskeleton through its interactions with α-, β-, γ- and p120-Catenin (19) (Figure 1). In contrast, TJs are made by the homophilic interaction of cell adhesion molecules such as Claudins, Occludin and Junction Adhesion Molecules (JAMs), which are connected to the actin cytoskeleton through *Zona Occludens* (ZO)-1, -2 and -3 proteins (Figure 1). Because of their importance, the establishment and maintenance of cell-to-cell junctions are tightly controlled. One of the best illustrations of such regulation is the modulation of vessel permeability by the Vascular Endothelial Growth Factor (VEGF) (20, 21). Its binding to Vascular Endothelial Growth Factor

97 Receptor (VEGFR)-2 induces an increase in intracellular calcium levels, leading to
98 the subsequent activation of Src family kinases, MAP kinases, PI3 kinase and protein
99 kinase G (21, 22). This mainly results in *i)* the remodeling of the actin cytoskeleton,
100 through the activation of the small GTPase Rho-A, *ii)* the activation of myosin light-
101 chain kinase (MLCK) that favors actomyosin contractility, *iii)* the destabilization of
102 integrin-mediated adhesion to the extracellular matrix and *iv)* the phosphorylation of
103 VE-Cadherin and its internalization, thus loosening cell-cell junctions (23). All
104 combined, these events participate in increasing endothelial permeability. In contrast,
105 the activation of other small GTPases, such as Rac-1 or Cdc42, protect the barrier
106 function of the endothelium by stabilizing intercellular junctions and the cortical actin
107 cytoskeleton (24). Therefore, the fine regulation of the interface between intercellular
108 junctions and the actin cytoskeleton plays a crucial role in regulating endothelial
109 integrity.
110 Strikingly, certain pathogens have the ability to overcome the physical barrier
111 imposed by the endothelium either from the outside towards the inside or/and vice
112 versa to exit the vascular lumen and reach specific organs. Pathogenic bacteria can
113 reach the circulation by accessing the vascular lumen through micro-abrasions within
114 the skin or mucosa but also through insect bites (25-27). Once in the circulation,
115 bacterial adhesion to the endothelium is a frequent starting point (28-30). Bacteria
116 then either divert the host cell actin cytoskeleton to induce their internalization and
117 transcytosis, leading to the passage of live bacteria through endothelial cells (31-35),
118 or remain extracellular and interfere with the assembly of intercellular junctions
119 facilitating their paracellular passage (36).
120

121 Hence, bacterial interaction with the endothelium often leads to the alteration of
122 vascular integrity that might be at the origin of vascular leaks, bacterial dissemination
123 within the surrounding tissues and/or organ dysfunction.
124 Throughout different examples of infection, we will here illustrate the many faces of
125 bacteria-endothelium interactions and the subsequent perturbations of specific
126 vascular functions in the particular environment of the blood circulation.
127

128 **ALTERATION OF VASCULAR INTEGRITY UPON INFECTIONS BY *RICKETTSIA***

129 Spotted fevers associated with rickettsial infections are among the best characterized
130 examples of pathogenic bacteria with a vascular tropism and disturbing endothelial
131 functions. Members of the *Rickettsia* family are obligate intracellular vector-borne
132 pathogens mainly transmitted by tick bites and triggering diverse diseases such as
133 typhus or spotted fever (27). Endothelial cells of the peripheral circulation represent
134 the main target of *Rickettsia* belonging to the spotted fever group (27, 37, 38) (Figure
135 2). *Rickettsia* adhesion to the endothelial surface is mediated by the expression of
136 the outer-membrane protein (Omp)-A and B (39) and their interaction with endothelial
137 integrins, such as the $\alpha_2\beta_1$ integrin (40). This induces a rapid and efficient
138 internalization of the adherent bacteria within few minutes after the initial contact.
139 Internalization occurs through a mechanism called "*induced phagocytosis*" that is at
140 the crossroad between phagocytosis and endocytosis (41, 42) and involving Clathrin
141 and Caveolin-2, two canonical proteins of the endocytic pathway (43).
142 Adhesion of *Rickettsia* onto endothelial cells also leads to a drastic remodeling of the
143 actin cytoskeleton within the host cells that not only facilitates bacterial entry but also
144 participates to bacteria movement and spreading within the endothelium. Endothelial
145 cell surface-bond bacteria locally regulate actin rearrangements by recruiting the

146 Arp2/3 complex and activating Cdc42 and kinases of the Src-family to support
147 bacterial internalization within phagosomal vesicles (44). The expression of the pore-
148 forming proteins Hemolysin C and Phospholipase D by *Rickettsia* allows them to
149 escape phagosomes and access the host cell cytosol (45-47) where they benefit
150 from nutrients and energy present to support their growth (48). Within infected cells,
151 *Rickettsia* also uses proteins from the actin cytoskeleton to propel and disseminate
152 within adjacent endothelial cells. *Rickettsia* assembles polar actin tails made of
153 unbranched parallel actin filaments, which help intracellular bacterial movement (49).
154 The precise machinery allowing bacteria to assemble these actin comet tails remains
155 debated. Whereas the involvement of RickA, a WASP-family protein homolog
156 encoded by *Rickettsia*, in Arp2/3-mediated actin polymerization *in vitro* favors a
157 mechanism of tail assembly relying on Arp2/3 activity (50, 51), Arp2/3 was not found
158 to associate with *Rickettsia* actin tails (52, 53). An alternative hypothesis rather
159 suggests that the bacterial protein Sca2 might participate in assembling actin tails
160 through a formin-like mechanism (54, 55).
161 The infection of endothelial cells by *Rickettsia* leads to the activation of the
162 endothelium, which is associated with the upregulation and secretion of a plethora of
163 cytokines and chemokines, collectively referred to as *rickettsial vasculitis* (56).
164 Interestingly, *Rickettsia* has developed different strategies to counteract immune
165 responses and optimize their intracellular residence. First, *Rickettsia* has the ability to
166 escape phagosomal vesicles before their fusion with lysosomes, hindering their
167 degradation by the lysosomal content (47). Moreover, the bacterium activates the
168 anti-apoptotic NF-κB signaling pathway within infected cells (57-60), thus balancing
169 the killing of these cells mediated by the recruitment of CD8 T cells (61).

170 Importantly, *Rickettsia* also damages the endothelium by altering the assembly of
171 endothelial intercellular junctions, most probably by disturbing the actin cytoskeleton
172 (62), as well as by inducing an oxidative stress within infected cells that contributes to
173 cell death (63, 64). Therefore, rickettsial infections lead to endothelial cell activation
174 and dysfunction, including an alteration of the vascular integrity that results in the
175 increase in vascular permeability and concurring to the pathophysiology of *Rickettsia*-
176 induced vascular leaks (56, 65). Despite alterations in vascular integrity, rickettsial
177 infections are not associated with subsequent dissemination to other organs, such as
178 the brain as in the case of meningitis-causing pathogens.
179

180 **VASCULAR COLONIZATION AND BLOOD-BRAIN BARRIER CROSSING BY**
181 ***NEISSERIA MENINGITIDIS***

182 A limited number of pathogenic bacteria have developed mechanisms allowing them
183 to cross the blood-brain barrier (BBB), most often triggering bacterial meningitis, a
184 high-fatality rate disease (66). A hallmark feature of the clinical manifestations of
185 bacterial meningitis is the presence of the pathogenic bacterium within the
186 cerebrospinal fluid (CSF) where it triggers the inflammation of the meninges and the
187 recruitment of immune cells within the CSF (66, 67). Since the bacterium is also
188 found in the bloodstream, the most prevalent view is that the bacterium breaches the
189 blood-CSF barrier to reach the CSF. However, as at this stage the anatomical site at
190 which crossing occurs is not known, we will rather refer to crossing of the blood-brain
191 barrier to be more inclusive.
192 With significant socioeconomic and geographic variations, *Neisseria meningitidis*,
193 *Streptococcus pneumoniae* and type B *Haemophilus influenzae* are the most
194 frequent causative agents of bacterial meningitis in adults and children. Of note,

195 while neonatal meningitis is mainly triggered by group B *Streptococcus*, *Listeria*
196 *monocytogenes* and *Escherichia coli* K1 (68), immunocompromised patients
197 frequently developed *Mycobacterium tuberculosis* or non-typhoid *Salmonella*
198 meningitis (69, 70). Despite their heterogeneity, common themes in the mechanisms
199 used by these pathogenic bacteria to cross the BBB can be drawn (for review, see
200 (71)).
201 Recent studies have pointed to the importance of a process called *vascular*
202 *colonization* during *N. meningitidis* infections and probably during meningitis (72).
203 This bacterium has the ability to adhere to the endothelial surface and proliferate in
204 the form of bacterial aggregates that eventually fill the lumen of small vessels of 10 to
205 50 µm in diameter (Figure 3). A recent study shows that this colonization process is
206 facilitated by the honey-like viscous liquid properties of the bacterial aggregates
207 which allow them to adapt to the complex morphology of the vasculature upon
208 proliferation (73). Adhesion to the endothelium likely participates in the immune
209 evasion as this prevents phagocytosis from Küpffer cells in the liver. Histological
210 analysis of *post-mortem* samples reveals large bacterial aggregates in the brain
211 vessels suggesting that vascular colonization could promote BBB crossing by
212 concentrating a high number of bacteria at specific sites and by altering endothelial
213 cell physiology (74). The combined effect of vessel occlusion due to bacterial
214 accumulation and the activation of the coagulation cascade (75) might participate in
215 altering endothelium integrity.
216 Alternatively, *in vitro* studies have identified specific signaling pathways triggered by
217 *N. meningitidis*, which lead to the opening of intercellular junctions within the cerebral
218 endothelium. Meningococcal adhesion to the host cells is mediated by their
219 expression of type four pili (Tfp) (76) that engage host cell surface receptors, such as

220 CD147 and β2-adrenergic receptor (77, 78). While proliferating at the surface of
221 infected endothelial cells, thus forming bacterial aggregates, meningococci induce
222 the remodeling of the host cell plasma membrane (79, 80) (Figure 3). Associated to
223 their aggregation capacity, plasma membrane protrusions infiltrating meningococcal
224 microcolonies were shown to enhance the mechanical cohesion of the microcolony
225 thus allowing them to resist the blood-flow induced shear stress (81). Interestingly,
226 although the cortical actin network is strongly reorganized below the bacterial
227 colonies (82), the active contribution of the host cells has been shown to be
228 dispensable in the *Nm*-mediated plasma membrane remodeling. The actin
229 cytoskeleton or even the intracellular ATP is not necessary for the Tfp-induced
230 plasma membrane reorganization (80, 81). Upon bacterial adhesion to microvascular
231 endothelial cells, Tfp trigger a complex cascade of signaling events leading to the
232 formation of "ectopic junctions" underneath bacterial aggregates together with the
233 local remodeling of the cortical actin cytoskeleton (83). This process relies, on the
234 one hand, on the activation of small GTPases such as cell division cycle protein 42
235 (Cdc42) and Rac1, along with the local recruitment of proteins of the polarity
236 complex, including partitioning-defective 3 (PAR3), PAR6 and protein kinase C-ζ
237 (PKC-ζ), as well as the branched-actin nucleating complex Arp2/3. On the other
238 hand, by mistargeting recycling endosomes, meningococci induce the accumulation
239 of junctional proteins, such as VE-Cadherin, underneath bacterial aggregates, a
240 process shown to weaken intercellular junctions and increase blood-brain barrier
241 permeability, thus facilitating meningococcal dissemination within the cerebral tissues
242 and the cerebrospinal fluid (CSF) (83). These elaborated mechanisms illustrate the
243 panoply of strategies enabling pathogenic bacteria to alter the endothelial barrier.
244

245 **ALTERATION OF THE ENDOCARDIUM AND ENDOCARDITIS**

246 Infective endocarditis (IE) is a bacterial infection of the cardiac endothelium. The
247 hallmark of IE is the colonization and destruction of the cardiac valves by pathogenic
248 bacteria following local endothelial injury or inflammation (84, 85) (for review, see
249 (86)). Although the causative agent of such a disease greatly varies according to the
250 geographic zones, most IE result from *Staphylococcus aureus*, *Enteroccocus* or
251 *Streptococcus* species, among which *S. gallolyticus* (87, 88).

252 The pathologic cascade starts following sterile lesions of the cardiac valve
253 endothelium of unclear origin that lead to the exposure of the extracellular matrix.
254 This triggers the formation of a platelet- and fibrin-rich thrombus, considered as a
255 hot-spot for the adhesion of blood-circulating bacteria (89) (Figure 4). Alternatively,
256 bacterial adhesion can occur at the surface of inflamed endothelium, a process
257 facilitated by the local upregulation of cell surface adhesion molecules, such as β1
258 integrins (90). From the bacterial side, adhesion is mediated by the surface
259 expression of extracellular matrix-targeting adhesins, such as fibronectin binding
260 proteins (FnBPs) (91, 92). Adherent bacteria locally proliferate and form a *vegetation*,
261 a biofilm-like structure where aggregated bacteria are mixed together with
262 extracellular matrix proteins, clot components and/or immune cells (93). While the
263 vegetation matures, the adjacent endothelial cells are exposed, thus driving the
264 propagation of the local inflammation and cell death and ultimately leading to the
265 destruction of the infected valves thus requiring surgical replacement (94). However,
266 this mechanism probably does not entirely account for IE induced by intracellular
267 bacteria such as *Bartonella* species or *Staphylococcus aureus*, which rather rely on
268 the secretion of exoenzymes and toxins to mediate their pathogenic effects (95) and
269 for which the host immune response might play an important role (96). Although

270 *Bartonella* species have been described in relatively rare cases of human
271 endocarditis (97, 98) with a preferential localization at the aortic valve (99), these
272 bacteria are mostly known for their involvement in angioproliferative syndromes.
273

274 **ANGIOPROLIFERATION DURING *BARTONELLA* INFECTIONS**

275 As mentioned earlier, angiogenesis supports the formation of new blood vessels from
276 pre-existing ones (12). Interestingly, this process can be diverted by pathogenic
277 bacteria and especially *Bartonella henselae* (for review, see (100)). *Bartonella spp.*
278 are Gram-negative organisms found in domestic and wild mammals with a tropism
279 for red blood cells and endothelial cells (100, 101). While in healthy individuals,
280 *Bartonella henselae* infections cause benign cat scratch diseases (102), in
281 immunocompromised patients these infections can trigger a vasoproliferative
282 syndrome resulting in the formation of tumor-like nodules in the skin, known as
283 cutaneous bacillary angiomatosis (BA) (100). This results from the ability of
284 *Bartonella henselae* to invade endothelial cells and trigger their proliferation and
285 migration (103, 104) together with the recruitment of macrophages, monocytes and
286 polymorphonuclear neutrophils (105, 106) (Figure 5).
287 Interestingly, similar to *Neisseria meningitidis* microcolonies, *B. henselae* also forms
288 plasma membrane-associated bacterial aggregates that either remain at the surface
289 of or are internalized in infected endothelial cells (106). Two actin-dependent
290 mechanisms have been described regarding bacterial internalization within
291 endothelial cells (107, 108): the first one is reminiscent of the previously described
292 bacterium-induced phagocytosis and allows the relatively fast entry of *Bartonella*
293 within perinuclear phagosomes (109). The second mechanism, lasting for up to 24
294 hours, allows the slow internalization of small *B. henselae* aggregates within large

295 vacuoles, referred to as invasomes (107). Of note, similarly to the protective
296 mechanisms developed by *Rickettsia* to promote their survival during their
297 intracellular residence, *Bartonella* is able to inhibit key steps of the apoptosis
298 program induced upon cell infections (110).
299 Although not fully understood, the proliferation of infected endothelial cells is in part
300 supported by bacterial proteins that are translocated within the host cells through the
301 VirB-VirD4 type IV secretion system (T4SS) encoded by *Bartonella* (111, 112). In
302 addition, several reports have shown that macrophages, locally recruited upon
303 endothelial cell infection, participate in the pathological angiogenesis induced by
304 *Bartonella*. Indeed, macrophages are well-known producers of pro-angiogenic factors
305 upon activation (113). *In vitro*, macrophages have been shown to support endothelial
306 proliferation through the secretion of VEGF in response to *B. henselae* infection (114,
307 115), thus suggesting that macrophages are involved in a paracrine loop that
308 enhances *Bartonella*-mediated vasoproliferation (116).
309

310 **SYSTEMIC IMPLICATIONS OF VASCULAR INFECTIONS**

311 Under steady-state conditions, besides normal transitory bacteremia, the vascular
312 organ is thought to be sterile (26). Therefore, it possesses robust mechanisms to
313 recognize circulating pathogens and trigger innate and/or adaptive immune
314 responses (117, 118). Similarly to immune cells specialized in pathogen recognition,
315 endothelial cells express chemokine receptors, such as CXCR-1, -2 and -4 (119,
316 120) as well as pattern-recognition receptors (PRRs), such as Toll-Like Receptors
317 (TLRs) and NOD-Like Receptors (NLRs) (121, 122). They have also been shown to
318 secrete pro-inflammatory molecules, such as the cytokines interleukin (IL)-1 and -8
319 (123-125) and to respond to bacterial lipopolysaccharide (LPS), tumor necrosis

factor-α (TNF-α) or interferon-γ (INF-γ) by signaling through the canonical pro-inflammatory NF-κB pathway (126). Hence, the endothelium possesses an array of tools allowing the recognition of pathogenic microorganisms and the recruitment of cells from the innate immune system in order to clear blood-circulating pathogens.

Of particular interest, endothelial cells (ECs) also participate in mounting adaptive immune responses since they can act as antigen presenting cells (APCs) (127). The hallmark of APCs is their expression of major histocompatibility complex class II (MHC-II) molecules allowing them to present extracellular antigens to T cells (128). Whereas quiescent ECs express basal levels of MHC-II molecules (129), they possess the capacity to upregulate their expression upon activation (130), providing them with the ability to present antigenic determinants to T cells and rapidly initiate pathogen-specific immune responses. Therefore, endothelial cells are equipped to recognize pathogenic microorganisms, locally attract cells of the innate immunity and serve as a link to trigger adaptive immune responses in order to efficiently fight invaders (for review, see (131)).

Although invasion of the endothelium by bacteria leads to the activation of the immune system, in absence of appropriate treatments or when the body fails clearing the pathogens, it might evolve toward an uncontrolled and systemic affection. Indeed, the constant release of damage-associated molecular patterns (DAMPs) by invading bacteria and/or injured endothelium leads to the imbalance of various body systems, among which the overstimulation of immune cells through TLRs and the complement pathway (132), as well as the exacerbated production of cytokines, referred to as the *cytokine storm* (133). Together with a persistent bacteremia, this systemic inflammatory response syndrome (SIRS) is the hallmark of sepsis (134, 135).

344 Paradoxically, a common feature of sepsis is its association with a form of immune
345 suppression occurring after the unregulated inflammation (132, 136). While not fully
346 understood, sepsis is marked by the severe depletion of T and B cells, as well as
347 dendritic cells, which all show an enhanced pro-apoptotic activity (137, 138). In
348 addition, in patients suffering from sepsis, a bias in the ratio of regulatory over
349 effector T cells is often observed (138, 139). The latter also showing a reduced ability
350 to produce cytokines, a feature known as T cell exhaustion (140), most probably due
351 to dysregulations in the programmed cell death 1 (PD1) - PD1 ligand 1 (PDL1) axis
352 (141), owing to the exacerbated cytokine production.
353 In addition, sepsis frequently affects the coagulation pathway: ranging from the
354 formation of small thrombi to the manifestation of disseminated intravascular
355 coagulation (DIC) –which corresponds to the coagulation of the blood throughout the
356 entire body– coagulopathies are one of the major complications in sepsis and have
357 been extensively reviewed elsewhere (142, 143). Nevertheless, we would like to
358 mention that perturbation of the coagulation pathway occurs early during sepsis and
359 first results from the activation of the endothelium in response to the cytokine storm,
360 thus favoring the local deposition of fibrin at the surface of the vessel walls (133).
361 Alternatively, endotoxins derived from Gram-negative bacteria, such as the
362 lipopolysaccharide (LPS), can trigger in a NF-κB-dependent manner both the
363 secretion and the surface expression of tissue factor (TF) by endothelial cells and
364 circulatory blood cells. By making a complex with the activated coagulation factor VII
365 (FVIIa), TF is a highly potent pro-coagulant molecule (144, 145). In both scenarios,
366 thrombus formation in turn leads to the activation of the endothelial cell surface
367 protease-activated receptor (PAR)-1 that signals through the small GTPase RhoA to
368 disassemble actin filaments and induce VE-Cadherin internalization, hence affecting

369 the stability of intercellular junctions and the integrity of the vascular endothelium
370 (118). As a consequence, vessels become leaky, blood pressure decreases and
371 proteins from the endothelial extracellular matrix, such as collagen, are exposed to
372 the vessel content, which further activates platelet aggregation and fibrin formation
373 (118, 143). Multi-organ failure is often associated with the late phases of DIC, which
374 results from microvascular thrombosis and poor tissue perfusion (146, 147).
375

376 **CONCLUDING REMARKS**

377 Bacterial infections taking place in the circulation are particularly problematic
378 because of the specific alterations they cause to the circulation, possibly affecting the
379 entire body. According to the specific site of infection and the properties of the
380 different pathogens, a complex set of interactions takes place during these infections.
381 Blood vessels are highly diverse with broad ranges of size and structure and each
382 pathogen has a set of virulence factors that alter blood vessel function in specific
383 ways. As a result, clinical manifestations are also very different. However, despite
384 this diversity, the endothelium is at the center of these infectious processes and a
385 limited number of endothelial functions are targeted in these infectious contexts: the
386 integrity of the vasculature and its permeability, but also its inflammatory and
387 coagulation status. More research is needed on host-pathogen interactions during
388 these systemic infections and on endothelial cell biology to better treat these
389 infections.
390
391
392
393

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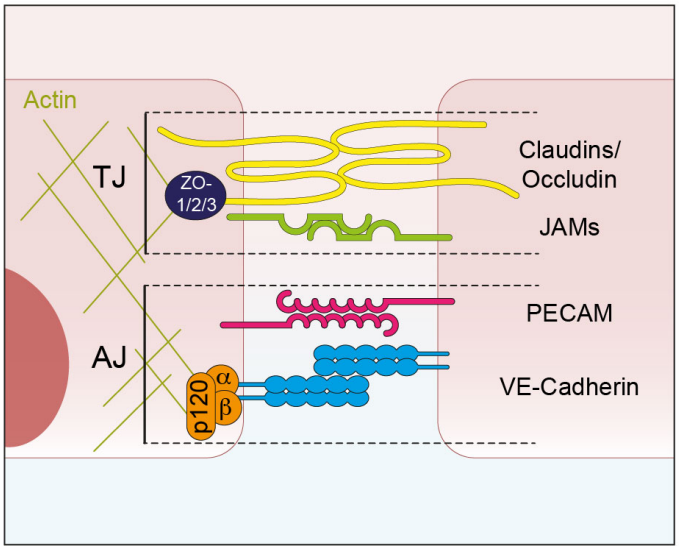
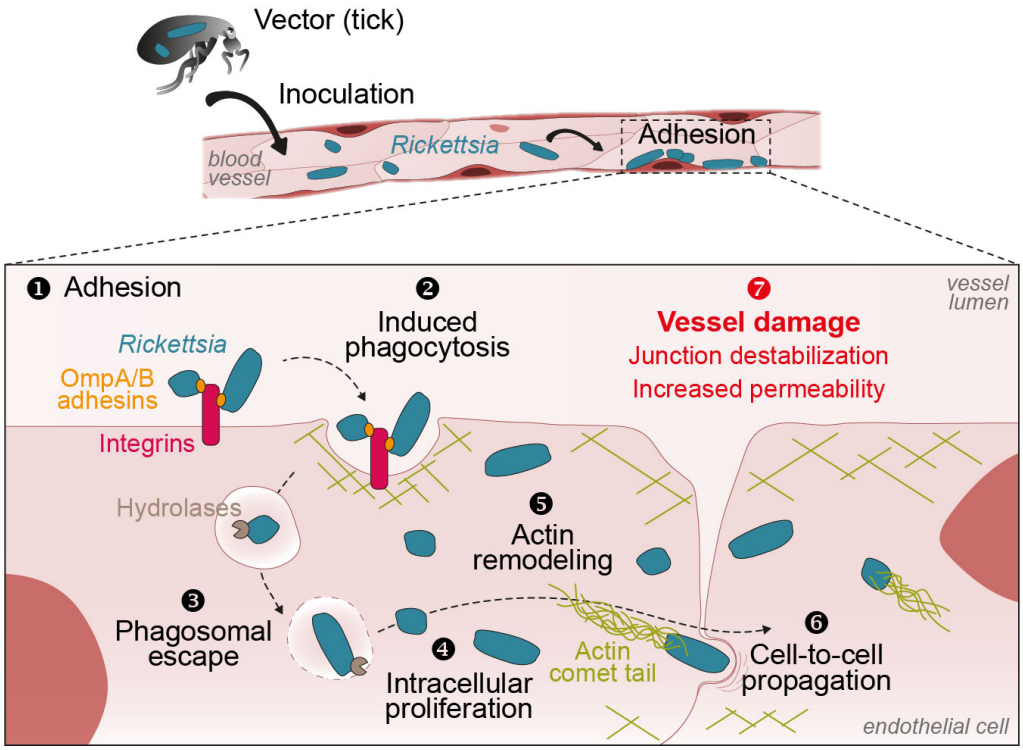


Figure 1: Schematic representation of the two main types of intercellular junctions within the endothelium. *Adherens* junctions (AJ) are made by the homophilic interaction of Vascular Endothelial (VE)-Cadherin and PECAM (Platelet endothelial cell adhesion molecule, also known as CD31). In contrast, claudins, occludin and proteins from the junctional adhesion molecules (JAMs) family are involved in establishing tight junctions. Connection with the actin cytoskeleton is ensured by proteins of the catenin family (alpha-, beta- and p120-catenin) in the case of *adherens* junctions, and proteins from the zonula occludens family (ZO-1, -2 and -3) in the case of tight junctions.



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842 **Figure 2: Infection of the endothelium by *Rickettsia*.** Following bacterial
843 inoculation into the lumen of blood vessels, *Rickettsia* adheres at the surface of the
844 endothelium through the surface expression of the outer-membrane protein (Omp)-A
845 and -B. Binding of Omp-A/B to cell-surface integrins induces the phagocytosis of
846 bacteria and the remodeling of the cellular actin cytoskeleton. Then, Hemolysin C
847 and/or Phospholipase D-expressing bacteria escape phagosomal vesicles, proliferate
848 intracellularly and utilize cellular components, such as actin monomers and nutrients,
849 to assemble actin comet tails supporting bacterial movement and cell-to-cell
850 spreading. Both actin cytoskeleton remodeling and bacterial propagation participate
851 in damaging infected vessels, including the destabilization of cellular junctions
852 responsible for the increase in vessel permeability.

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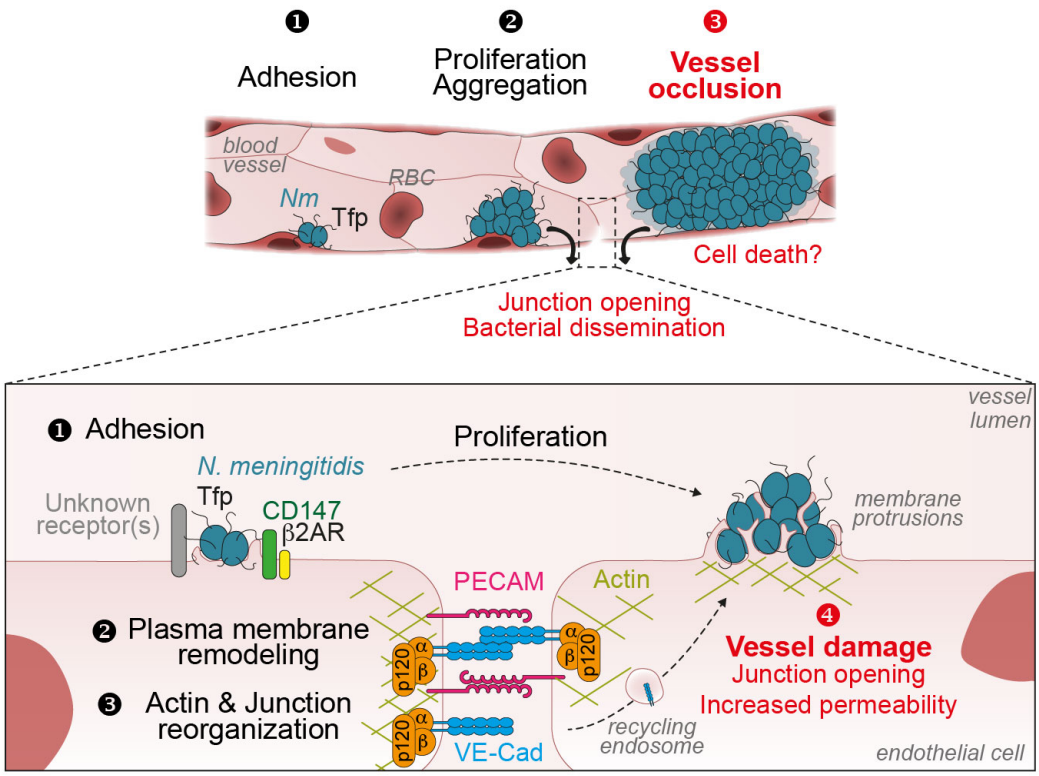

854

855 **Figure 3: Vascular colonization by *Neisseria meningitidis.*** Once into the
856 bloodstream, *Neisseria meningitidis* adheres to the endothelium thanks to the surface
857 expression of type four pili (Tfp). While proliferating, and owing to their auto-
858 aggregative property, bacteria form a tight microcolony at the surface of the
859 endothelium, which ultimately leads to the congestion of the colonized vessel.
860 Bacterial adhesion at the surface of endothelial cells induces a drastic remodeling of
861 the host cell-plasma membrane that forms membrane protrusions interdigitating
862 within the bacterial aggregate. In addition, pilus interaction with endothelial cell-
863 surface receptors, such as CD147 or β2-adrenergic receptor (β2-AR), induces the
864 reorganization of the actin cytoskeleton and intercellular junctions by recruiting their
865 components underneath the microcolony. Taken together, these events are proposed
866 to destabilize intercellular junctions, hence resulting in the increase in vessel
867 permeability.

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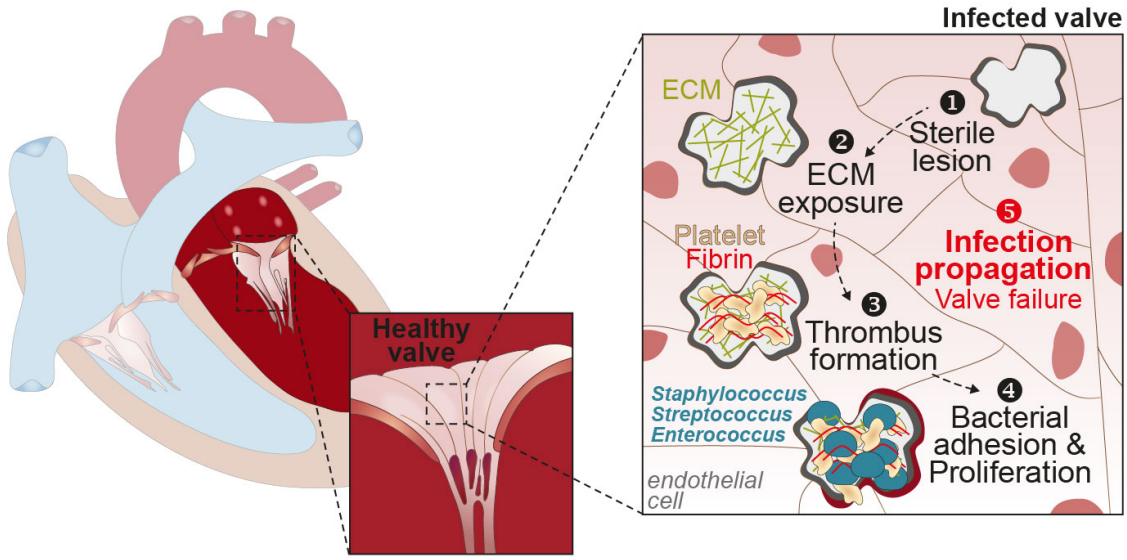

869

870 **Figure 4: The stepwise process leading to endocarditis.** The apparition of sterile
871 lesions (most often of unknown origin) on the heart valvular endothelium leads to the
872 exposure of the underneath extracellular matrix (ECM). This in turn triggers the
873 formation of a thrombus – characterized by the local deposition of platelets and fibrin
874 at the surface of the damaged endothelium – that favors bacterial adhesion. While
875 bacteria proliferate and spread, the valvular endothelium become more and more
876 damaged, eventually leading to the failure of the valve and the need for its surgical
877 replacement.

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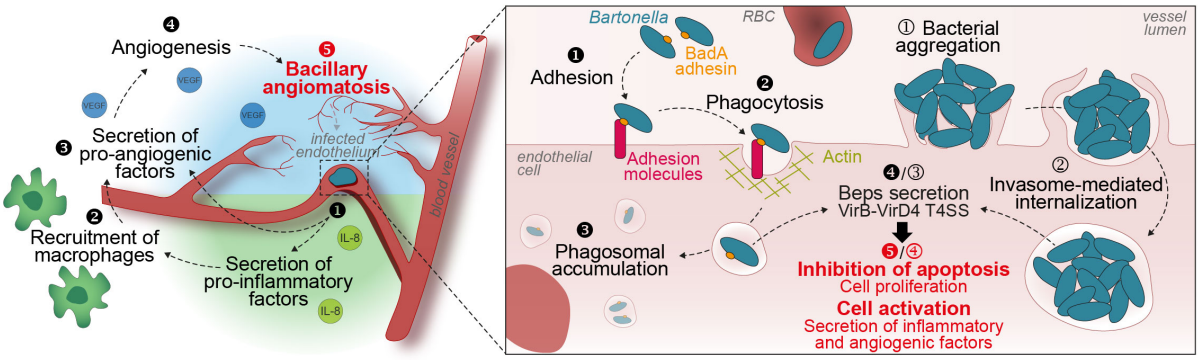

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880 **Figure 5: *Bartonella*-induced angioproliferation.** Interactions of *Bartonella* with the
881 endothelium might occur at the single-bacterium level through the bacterial
882 expression of the Bartonella adhesin A (BadA) protein. This triggers the phagocytosis
883 of the cell-surface bound bacteria and results in their perinuclear accumulation within
884 phagosomes. Similarly, to *Neisseria meningitidis*, *Bartonella* also forms aggregates
885 that are internalized through a slower process within big vacuoles, referred to as
886 invasomes. In both cases, the VirB-VirD4 type four secretion system (T4SS)-
887 dependent cytoplasmic release of *Bartonella* effector proteins (Beps) by intra-
888 vesicular bacteria promotes the proliferation and activation of the infected endothelial
889 cells. This notably results in the secretion by the endothelium of pro-inflammatory
890 (*e.g.* IL-8) and pro-angiogenic (*e.g.* VEGF) factors. As a consequence, cells from the
891 innate immunity, including neutrophils and macrophages, are locally recruited to fight
892 the infection. Activated macrophages locally secrete VEGF, thus reinforcing the pro-
893 angiogenic microenvironment. Combined to the bacterium-mediated endothelial cell
894 proliferation, this particular environment promotes angiogenesis that ultimately leads
895 to the local accumulation of new blood capillaries and the formation of Bacillary
896 Angiomatosis lesions.