Role of oral pathogens in the pathogenesis of intracranial aneurysm: review of existing evidence and potential mechanisms

Joona Hallikainen1,2,3,7 · Sara Keränen3 · Jarno Savolainen1,2 · Matti Närhi1,4 · Anna Liisa Suominen1,2,5 · Pekka Ylöstalo6 · Jari Kellokoski1,2 · Mikko Pyysalo7 · Pirkko Pussinen8 · Tuomas Rauramaa9 · Juhana Frösen3,7,10

Received: 24 November 2019 / Revised: 12 January 2020 / Accepted: 27 January 2020 / Published online: 7 February 2020 © The Author(s) 2020

Abstract
Degeneration of intracranial aneurysm wall is under active research and recent studies indicate an increased risk of rupture of intracranial aneurysm among patients with periodontal diseases. In addition, oral bacterial DNA has been identified from wall samples of ruptured and unruptured aneurysms. These novel findings led us to evaluate if oral diseases could predispose to pathological changes seen on intracranial aneurysm walls eventually leading to subarachnoid hemorrhage. The aim of this review is to consider mechanisms on the relationship between periodontitis and aneurysm rupture, focusing on recent evidence.

Keywords Intracranial aneurysm · Periodontitis · Pathogens · Oral diseases · Subarachnoidal hemorrhage

Introduction
Recently, our group found the association with periodontitis, formation of intracranial aneurysms (IA), and the risk of aneurysmal subarachnoid hemorrhage (aSAH) [25]. Together with the prior reports that DNA of oral bacteria is found in the wall of many ruptured intracranial aneurysms [64, 65], these results raised the intriguing question whether periodontitis and oral bacteria participate to the formation of IAs and to their progression towards rupture. We review the current research about the association of oral infections with aneurysms and other vascular diseases, and discuss the potential mechanisms by which oral infections may modulate, contribute to, or even cause the degenerative remodeling of the aneurysm wall and as such predispose to the risk of aneurysmal subarachnoid hemorrhage.

Intracranial aneurysms as a clinical challenge—need for identification of rupture-prone aneurysms
Intracranial aneurysms (IA) are pathological dilatations of cerebral arteries, most often saccular in shape and frequently found in proximal cerebral artery bifurcations [30]. Aneurysms are relatively common with a prevalence of 2–3% in the general population [70, 91]. Although unruptured IAs are common, intracranial hemorrhage caused by IA rupture is a quite rare event affecting 10–11/100000 population per year in Western populations [32]. In fact,
based on epidemiological data, it seems that only approximately 1% of IAs rupture per year [70] and many of them actually never rupture during the lifetime of the person carrying them [41]. However, because of the serious consequences that IA rupture and subsequent intracranial hemorrhage have (40% mortality and most of the survivors being left with significant neurological impairment [54, 78]), many of the diagnosed unruptured IAs are treated to prevent rupture. Preventive treatment is done by endovascular embolization of aneurysm sack or by microsurgical ligation of the aneurysm neck, both of which exclude the aneurysm from systemic circulation. Both of the current treatment options are associated with significant risk of serious neurological complications (5–7%), including mortality (1–2%) [43, 53]. Therefore, it is paramount to focus intervention only to those IAs at risk of rupture. This remains a challenge.

The discrepancy between the relatively high prevalence of unruptured IAs and the low incidence of IA rupture, together with the observation that only 1/3 of unruptured IAs ruptured during a life-long follow-up [41], strongly suggests that IA formation and IA rupture are two separate phenomena with different pathological background. Moreover, these observations suggest that while some IA walls are able to adapt to the mechanical load imposed on them, in others degenerative remodeling makes the IAs rupture-prone. This in turn implies that by pharmacological manipulation of the adaptive or degenerative remodeling of the IA wall, it might be possible to keep the formed unruptured IAs stable and prevent rupture. To achieve this, the pathophysiological mechanisms guiding IA growth and rupture, i.e., adaptive and degenerative wall remodeling, need to be understood. Moreover, biomarkers for an IA wall capable of adaptive remodeling are needed to identify those IAs that can be stabilized with drug therapy.

**Intracranial aneurysms show chronic inflammation that is associated with wall degeneration and rupture**

Since human tissue samples from the site of IA initiation are inherently difficult to obtain, most of our knowledge of the pathophysiological mechanisms leading to IA formation is derived from animal models of induced IA formation [1, 27, 34, 39]. Current understanding is that IAs form as the end result of flow-driven inflammatory cell-mediated cerebral artery wall remodeling at the sites where high flow causes high wall shear stress (WSS) [22, 75] (Fig. 1). However, not all cerebral artery bifurcations exposed to high WSS develop IAs, suggesting that additional factors are needed [22]. A common feature to IA initiation is the disruption of internal elastic lamina (IEL) [27, 39], resulting in distension of the vessel wall to the extent that collagen fibers allow [22]. In a mouse model of induced IA formation, IEL disruption is related to flow-induced macrophage infiltration [22, 34]. In humans, however, systemic elastase activity may play a significant role since increased serum elastase concentrations associate with IAs [10], although the source is unknown. Potential sources for circulating elastase are macrophages or neutrophils [13, 68]. Given that chewing or brushing teeth predisposes to transient bacteremia, especially in patients with gingivitis or periodontitis [16, 28, 49, 84], activation of circulating neutrophils as a response to transient bacteremia of periodontal pathogens with subsequent formation of neutrophil extracellular traps (NETs) and elastase release [13] could lead to wall degeneration (Fig. 2)—thus explaining why IA form for some but not all persons under high flow and shear stress towards bifurcations of cerebral arteries [75].

In humans, increased infiltration of leukocytes, mainly macrophages and to some extent T-cells, is observed in ruptured IA walls compared with unruptured IA walls [18, 37, 55]. The observation that inflammatory cell infiltration is present in unruptured IAs as well as in ruptured IAs operated early after rupture, combined with the observation that this inflammatory cell infiltration does not associate with time from rupture [18], strongly implies that the inflammatory cell infiltration is present before rupture. Thus, inflammatory cell infiltration associates with wall degeneration in both unruptured and ruptured IA walls [56, 57]. In animal models of induced IA formation, blocking macrophage infiltration or activation inhibits the formation, growth, and rupture of the IAs [2, 3, 36, 74].
Inflammatory response mediated especially by macrophages is an essential part of the flow-induced vessel remodeling that leads to aneurysm initiation and growth [22]. However, in the human IA wall also a humoral immune response and activation of the complement system are observed and associating with wall degeneration in unruptured IA walls as well as with rupture [86, 87]. This strongly implies that the chronic inflammation seen in human IA walls is not just related to flow-induced remodeling, especially since there is very high variation in the inflammation degree among IAs [18, 55, 86] despite the fact that all are exposed to non-physiological flow. The cause of this inflammation in the IA wall is unclear.

Potential triggers of inflammation include circulating lipids [20, 88] and periodontal and cariogenic bacteria [31, 64, 65].

The highly prevalent oral infections, dental caries and periodontitis, and their systemic effects

Dental caries and periodontitis are both highly prevalent oral diseases worldwide despite the modern dental therapy and accumulating knowledge of oral diseases. Caries is an infectious disease of hard tissues of the tooth, and the prevalence of untreated caries is one-third of the global population as well as in Europe [17] in the USA and Asia pacific, the prevalence varies between 22 and 25% [17]. Another common oral disease, periodontitis, is also to a large extent preventable inflammatory disease and highly underdiagnosed. Its severe form affects about 10% of the global population, and 7% in Asia pacific area [17]. In the USA, the prevalence of mild to moderate and severe periodontitis is reported to be 46% and 9% of adults, respectively [14]. In Europe, corresponding prevalence is 40–60% and 10–20% [17], respectively.

The microbial load on tooth surface, dental plaque, composed of hundreds of microbial species [59]. Periodontal pathogenesis initiates by microbial accumulation on the tooth surface resulting a reversible gingival inflammation known as gingivitis [77, 83], which may progress to periodontitis among susceptible individuals when the normally dominating beneficial species become lessened and replaced by pathogenic species [40]. Therefore, endured microbial burden, in form of dental plaque or calculus, leads to a chronic inflammatory disease—periodontitis. Without interventional therapy, periodontitis leads to breakdown of both soft and hard tissue mainly via inflammatory host response [11] causing loss of tooth attachment and eventually loss of alveolar bone in the jaws. Periodontitis not only degenerates tooth surrounding structures but affects the inflammatory system [35, 51, 52, 60, 62] and systemic health [12, 25, 38, 45, 46, 63, 79].

Periodontitis is associated with the risk of several diseases. For example, in rheumatoid arthritis, Porphyromonas gingivalis (PG), one of the most common periodontal pathogens, seems to be potential generator of autoantibodies [50]. Periodontitis has also been associated with atherosclerosis, stroke [38, 46, 63], and abdominal aortic aneurysms (AAA) [12, 45, 79]. Very recently, our group showed that periodontitis or gingivitis associate also with aSAH and IA formation [25]. In addition to this, another recent study reported an association between aSAH and being a carriage of specific strains of Streptococcus mutans, a significant contributor to tooth decay [31]. These clinical studies suggest that oral infections and exposure to oral pathogens associate with risk of IA formation and aSAH.

Potential role of periodontal pathogens in the pathobiology of the intracranial aneurysm

In addition to the clinical association of periodontitis with IA formation and aSAH suggesting a potential causative association, a recent experimental study has reported that temporary ablation of the gut microbiome prevents IA formation through indirect...
modulation of the inflammatory remodeling in the cerebral arteries [21, 73]. This experimental study highlights the thus far unnoticed importance of microbial exposure in the pathogenesis of IAs.

While it has been long known that septic, bacterial emboli ending up in cerebral arteries may cause formation of so-called mycotic aneurysms through focal inflammation of the artery wall, most saccular IAs have been considered as being aseptic. However, a landmark study screening human IA wall tissue samples for the presence of any bacterial DNA demonstrated DNA of oral pathogens in up to 50% of ruptured IA walls [64, 65]. The fact that the remaining 50% were negative for any bacterial DNA demonstrates that IAs can form without direct bacterial involvement. The combination of having an epidemiological association between periodontal infection and IA formation and rupture [25, 66], experimental proof that microbiome exposure modulates IA formation [21, 73], and that even presence of oral pathogen remnants is found in many IA walls [64, 65] justifies the hypothesis that periodontal pathogens contribute to the risk of IA formation and rupture through indirect or direct modulation of the inflammatory remodeling in the cerebral artery and IA wall.

Potential mechanisms through which oral pathogens can affect inflammatory remodeling in the IA wall

We will focus on those periodontal pathogens that have been identified in walls of ruptured intracranial aneurysms by Pyysalo et al. [64, 65] and discuss through their known role in other vascular diseases their potential contribution to IA pathogenesis.

The importance of macrophage infiltration for the inflammatory remodeling leading to IA formation has been demonstrated by several studies [3, 22, 36, 74, 80], including the landmark experimental studies by Kanematsu et al., Shimada et al., and Aoki et al. [3, 36, 74]. P. gingivalis can stay viable in human macrophages and dendritic cells [7, 76, 92] and thus possibly disseminate to IA wall via macrophage infiltration. P. gingivalis seems to be capable of modifying the function of dendritic cells, for example, the secretion of collagen degrading MMP-9 is promoted in dendritic cells that are infected with P. gingivalis [7]. In addition, presence of P. gingivalis and Fusobacterium nucleatum (FN) DNA has shown to induce proinflammatory cytokine production in macrophages [71, 72]. Thus P. gingivalis infection of the macrophages that infiltrate the cerebral arteries would likely lead to excessive collagen degradation and local inflammation response, predisposing to IA formation.

Another mechanism through which circulating components of oral bacteria could enhance or amplify the inflammatory remodeling of the cerebral artery wall is through activation of toll-like receptors by LPS, e.g., from P. gingivalis in luminal thrombus [12] (Fig. 3). Toll-like receptors are expressed in aneurysm walls [64] and their stimulation triggers activation of the transcription factor NFkB [3], a main mediator of the inflammatory remodeling leading to IA formation [3]. As a result, having oral bacteria-derived components in the circulation would promote inflammatory vessel remodeling triggered by, e.g., high flow, and thus predispose to IA formation.

Viable periodontal bacteria, namely P. gingivalis, Aggregatibacter actinomycetemcomitans (AA), and Treponema denticola (TD), have been found in human atheromas [8, 44, 67] (Fig. 4). In vitro and in vivo studies have well established that it is biologically plausible that periodontitis accelerates atherosclerosis [6, 33, 48, 69]. Recent mechanistic study using ApoE<sup>−/−</sup> mouse model revealed an ability of P. gingivalis to actively invade luminal side of aortic wall, retaining its vitality and leading to greater aortic plaque area [47, 90]. In another mechanistic study using a pig model, circulating P. gingivalis promoted atherosclerosis not only in hypercholesterolemic pigs but also normocholesterolemic ones [6]. These findings suggest that the active invasion of periodontal pathogens in the artery wall with or without presence of cholesterol can be a potential trigger of atherosclerotic activity. Nearly all intracranial aneurysms feature at least minor atherosclerotic changes and advanced atherosclerotic changes are seen in large numbers [20, 42]. Of note is that the accumulation of lipid and oxidized low-density lipoprotein (oxLDL) was found to associate with IA wall degeneration, loss of mural cells, and also IA rupture, despite normal lipid levels [20]. Interestingly, not only has P. gingivalis been shown to accelerate atherosclerosis [6, 90] but immunization against it has been shown to reduce atherosclerotic changes [24, 89]. Thus, accumulation of oxidized lipids to the IA wall and subsequent atherosclerotic remodeling might be altered indirectly by systemic immunization induced by local periodontitis. It seems possible that the presence of P. gingivalis in the IA wall or immune response induced by P. gingivalis elsewhere in the body may modulate directly or indirectly the progression of atherosclerotic changes and lipid-induced inflammation in the IA wall.

Periodontitis is common also among patients with abdominal aortic aneurysms (AAA) and periodontal bacterial DNA have been identified in AAA wall structure as well as in the thrombus lining the AAA inner wall [12, 45]. Presence of periodontal bacteria promotes AAA growth, i.e., enlargement of luminal diameter [4, 12], and thus could predispose AAA to rupture. P. gingivalis appears to promote AAA pathogenesis by maintaining inflammation and increasing oxidative stress in the AAA wall via adhesion to the intraluminal thrombus [12]. P. gingivalis has an affinity for thrombus and can passively accumulate to sites of thrombosis if it is present in the bloodstream [12]. In the thrombus, P. gingivalis is capable of inducing the formation of neutrophil-derived extracellular traps (NETs), which increases further the accumulation of neutrophils to the thrombus [12]. Fontaine et al. have shown that the neutrophils in the intraluminal thrombus are a major source of proteolytic activity as they release matrix metalloproteinases MMP-8, MMP-9, and elastase [15, 29]. Furthermore, the neutrophils attracted to luminal thrombus produce proteases and cytotoxic enzymes such as
myeloperoxidase (MPO) [15, 29], which generates, e.g., hydrogen peroxide and hypochlorous acid intended to kill bacteria and lead to very high oxidative stress locally [26]. In addition to increasing the local recruitment of neutrophils, P. gingivalis can also activate the neutrophils in the thrombus, thus accelerating the neutrophil-derived proteolytic and cytotoxic injury [12](Fig. 3). This cytotoxic injury is in part mediated by MPO. In summary, presence of P. gingivalis in the intraluminal thrombus or adjacent AAA wall can trigger or enhance the activation and recruitment of neutrophils, leading to excessive proteolytic and cytotoxic injury to the vessel wall. Similarly to AAAs, neutrophils are recruited to the luminal thrombus lining the IA walls.

**Fig. 3** High flow conditions stretch the vessel wall and induce monocyte chemoattractant protein 1 (MCP-1) in vascular smooth muscle cells (VSMC) attracting invading macrophages to vessel wall. Similar MCP-1 production is caused by lipopolysaccharide (LPS) production of periodontal bacteria via activating nuclear factor kB (NFkB) -signaling via toll-like receptors. These mechanisms lead to cyclo-oxygenase 2-prostaglandin E2-NFkB-cyclo-oxygenase 2 (COX2-PGE2-NFkB-COX2)-amplifying loop in IA wall and lead to proliferation of smooth muscle cells expanding the IA.

**Fig. 4** Periodontal bacteria have ability to dysregulate complement activity with their protease production (Porphyromonas gingivalis PG, Prevotella intermedia PI, and Tannerella forsythia TF) or directly binding complement factor C4bp and factor H (Porphyromonas gingivalis PG, Prevotella intermedia PI, Treponema denticola TD, and Aggregatibacter actinomycetemcomitans AAA). These bacteria simultaneously accelerate complement activity yet evade complement-mediated killing is unique and could partially explain inflammation in IA wall, especially since oral bacterial DNA is found in unruptured and ruptured IA walls.
[18, 19, 56]. Luminal thrombus is common in IAs [18], as is periodontitis in IA patients [25, 66] suggesting that P. gingivalis might accelerate neutrophil-driven thrombus-derived proteolytic and cytotoxic injury in the IA wall similarly to the AAA walls. Indeed, MPO expression has been demonstrated in human IA walls [23, 56] and locally higher MPO concentrations have been observed in serum from aneurysm sac than to femoral artery blood [9].

Besides the infiltration of inflammatory cells such as macrophages and neutrophils, activation of the complement system is involved in IA wall degeneration and rupture [86, 87]. It has been shown earlier that periodontal bacteria can dysregulate complement activity in vitro by binding to or degenerating complement factors [35, 51, 52, 60, 62]. Of periodontal pathogens, specific strains of Prevotella intermedia (PI) and P. gingivalis participate in complement activation by binding factor H [51] and C4bp respectively [61]. Treponema denticola (TD) and A. actinomycetemcomitans, common periodontal pathogens, have ability to bind factor H [5, 52]. These bacteria do not only dysregulate complement activity but also evade complement-mediated killing in response of binding factor H [51, 52]. It is noteworthy that DNA of both P. intermedia and T. denticola have been identified in some of ruptured IAs [64, 65]. Interestingly, P. gingivalis, P. intermedia, and Tannerella forsythia (TF) are capable of evading complement-mediated killing by altering complement activity and degenerating complement factors via their bacterial proteases, while protecting other bystander bacteria [35, 60, 62]. This ability of periodontal bacteria to activate complement while evading complement-mediated killing may in part explain the complement activation seen in the IA wall in association with IA wall degeneration.

In addition to the mechanisms described above, periodontal bacteria may also trigger IA wall degeneration via endothelial dysfunction, which seems to be one of the key events that triggers the lipid accumulation, luminal thrombosis, and inflammation that associate with the IA wall degeneration [19]. A recent meta-analysis concluded that periodontal bacteria predispose to endothelial dysfunction [58]. Moreover, endothelial dysfunction improves with periodontal treatment [58, 85]. Endothelial dysfunction can be at least in part caused by bacterial burden of periodontitis and furthermore, endothelial dysfunction could explain why periodontal IAs are often found in the sites of vascular diseases, e.g., IA walls and atheromas. Interestingly, periodontitis patients also have higher concentration of circulating oxidized LDL particles in the blood [81, 82], another mechanism more through which periodontitis can accelerate local atherosclerotic remodeling in the IA wall.

Conclusion

Although the association of aneurysm rupture with chronic inflammation of the aneurysm wall is well established, the triggers for this inflammatory reaction are incompletely understood. The recent finding that periodontitis or gingivitis associates with increased risk of aSAH together with DNA of oral bacteria found in the walls of many IAs raises the hypothesis that oral infections are related to the inflammation of the IA wall. In this review, we presented several mechanisms by which periodontitis and periodontal pathogens can contribute to the degenerative remodeling of the IA wall. These mechanisms merit further investigation and may reveal a previously unknown and treatable risk factor for the deadly aneurysmal subarachnoid hemorrhage.

Funding Information

Open access funding provided by University of Eastern Finland (UEF) including Kuopio University Hospital.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Open Access

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Aoki T, Nishimura M (2011, 2011: 535921) The development and the use of experimental animal models to study the underlying mechanisms of CA formation. J Biomed Biotechnol. https://doi.org/10.1155/2011/535921
2. Aoki T, Kataoka H, Ishitahi R, Nozaki K, Egashira K, Hashimoto N (2009) Impact of monocyte chemoattractant protein-1 deficiency on cerebral aneurysm formation. Stroke 40:942–951. https://doi.org/10.1161/STROKEAHA.108.532356
3. Aoki T, Frosen J, Fukuda M, Bando K, Shiio G, Tsuji K, Oikikainen E, Nozaki K, Laakkonen J, Naramiya S (2017) Prostaglandin E2-EP2-NF-kappaB signaling in macrophages as a potential therapeutic target for intracranial aneurysms. Sci Signal 10. https://doi.org/10.1126/scisignal.aab6037
4. Aoyama N, Suzuki J, Wang D, Ogawa M, Kobayashi N, Hanatani T, Takeuchi Y, Izumi Y, Isobe M (2011) Porphyromonas gingivalis promotes murine abdominal aortic aneurysms via matrix metalloproteinase-2 induction. J Periodontal Res 46:176–183. https://doi.org/10.1111/j.1600-0765.2010.01326.x
5. Asakawa R, Komatsuzawa H, Kawai T, Yamada S, Goncalves RB, Izumi S, Fujiwara T, Nakano Y, Suzuki N, Uchida Y, Oshara K,
Shiba H, Taubman MA, Kuniha H, Sugai M (2003) Outer membrane protein 100, a versatile virulence factor of Actinobacillus actinomycetemcomitans. Mol Microbiol 50:1125–1139

6. Brodala N, Merricks EP, Bellinger DA, Damronsgtr D, Offenbacher S, Beck J, Madians P, Sotres D, Chang YL, Koch G, Nichols TC (2005) Porphyromonas gingivalis bacteremia induces coronary and aortic atherosclerosis in normocolesterol and hypercholesterolemic pigs. Arterioscler Thromb Vasc Biol 25:1446–1451. https://doi.org/10.1161/01.ATV.0000167525.69400.9c

7. Carrion J, Scisci E, Miles B, Sabino GJ, Zeituni AE, Gu Y, Bear A, Genco CA, Brown DL, Cutler CW (2012) Microbial carriage state of peripheral blood dendritic cells (DCs) in chronic periodontitis influences DC differentiation, atherogenic potential. J Immunol 189:3178–3187. https://doi.org/10.4049/jimmunol.1201053

8. Cavrini F, Sambri V, Moter A, Servidio D, Marangoni A, Montebugnoli L, Boschi F, Prati C, Di Bartolomeo R, Cevenini R (2005) Molecular detection of Treponema denticola and Porphyromonas gingivalis in carotid and aortic atheromatous plaques by FISH: report of two cases. J Med Microbiol 54:93–96. https://doi.org/10.1099/jmm.0.45845-0

9. Chu Y, Wilson K, Gu H, Wegman-Points L, Dooley SA, Pierce GL, Montgomery KD, Shen CS, Lumsden RB, Wilson M, Trappenburg BM, Ooshima T, Kuriyama N, Hamasaki T, Wada K, Umemura K, Kurihara N, Kondo T, Yamazaki K, Yamamoto M (2014) Sublingual vaccine with GroEL attenuates atherosclerosis. J Dent Res 93:382–387. https://doi.org/10.1177/0022034514523784

10. Connolly ES Jr, Fiore AJ, Winfree CJ, Prestigiacoma CJ, Goldman JE, Solomon RA (1997) Elastin degradation in the superficial temporal arteries of patients with intracranial aneurysms reflects changes in temporal arteries of patients with intracranial aneurysms and resolves chronic and acute endovascular aneurysm remodeling in patients with chronic and acute endovascular aneurysm remodeling. Neurosurgery 40:903–909. https://doi.org/10.1097/00006123-199705000-00003

11. Darveau RP (2010) Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol 8:481–490. https://doi.org/10.1038/nrmicro2337

12. Delbosc S, Alsac JM, Courme C, Louedec L, Castier Y, Bonnare-Mallet M, Ruimy R, Rossignol P, Bouchard P, Michel JB, Meilhac O (2011) Porphyromonas gingivalis participates in pathogenesis of human abdominal aortic aneurysm by neutrophil activation. Proof of concept in rats. PLoS One 6:e18679. https://doi.org/10.1371/journal.pone.0018679

13. Delgado-Rizo V, Martinez-Guzman MA, Iniguez-Gutierrez L, Garcia-Orozco A, Alvarado-Navarro A, Fautitis-Morris M (2017) Neutrophil extracellular traps and their implications in inflammation: an overview. Front Immunol 8:81. https://doi.org/10.3389/fimmu.2017.000081

14. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, Taylor GW, Page RC, Beck JD, Genco RJ (2015) Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol 86:611–622. https://doi.org/10.1902/jop.2015.140520

15. Fontaine V, Jacob MP, Houard X, Rossignol P, Pannuti CM, Romito GA (2014) Dissemination of periodontal pathogens in the bloodstream after periodontal procedures: a systematic review. PLoS One 9:e98271. https://doi.org/10.1371/journal.pone.0098271

16. Forner L, Larsen T, Kilian M, Holmstrup P (2006) Incidence of periodontitis and gingival bleeding associate with intracranial aneurysms and risk of aneurysmal subarachnoid hemorrhage. Neurosurg Rev 30:90

17. Frösen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A, Niemela M, Hernesniemi J (2012) Saccular intracranial aneurysm: pathogenesis and mechanisms. Acta Neurochir 123:773–786. https://doi.org/10.1007/s00701-011-0939-3

18. Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemela M, Hernesniemi J, Jaaskelainen J (2004) Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. Stroke 35:2287–2293. https://doi.org/10.1161/01.ATV.0000140636.30204.da

19. Frösen J, Tulamo R, Heikura T, Sammalkorp I, Niemela M, Hernesniemi J, Levonen AL, Horkko S, Yla-Herttuala S (2013) Lipid accumulation, lipid oxidation, and low plasma levels of acquired antibodies against oxidized lipids associate with degeneration and rupture of the intracranial aneurysm wall. Acta Neurochir Commun 17:1. https://doi.org/10.1186/2051-5960-1-71

20. Frösen J, Hallikainen J, Pysyalo M, Koivist o T, Lindgren A (2019) Letter by Fro sen et al regarding article “potential influences of gut microbiota on the formation of intracranial aneurysm”. Hypertension 74:e22–e23. https://doi.org/10.1161/HY PertensionAHA.119.13253

21. Frösen J, Cebral J, Robertson AM, Aoki T Flow induced inflammation mediated artery wall remodeling in the formation and progression of intracranial aneurysms. Neurosurg Focus

22. Gounis MJ, Vedantham S, Weaver JP, Puri AS, Brooks CS, Wak hloo AK, Bogdanov AA Jr (2014) Myeloperoxidase in human intracranial aneurysms: preliminary evidence. Stroke 45:1474–1477. https://doi.org/10.1161/STROKEAHA.114.004956

23. Hagiwara M, Kurita-Ochiai T, Kobayashi R, Hashizume-Takizawa T, Yamazaki K, Yamamoto M (2014) Sublingual vaccine with GroEL attenuates atherosclerosis. J Dent Res 93:382–387. https://doi.org/10.1177/0022034514523784

24. Hallikainen J, Lindgren A, Savolainen J, Selander T, Jula A, Narhi M, Koivist o T, Kellokoski J, Ylostalo P, Suominen AL, Fro sen J (2019) Periodontitis and gingival bleeding associate with intracranial aneurysms and risk of aneurysmal subarachnoid hemorrhage. Neurosurg Rev. https://doi.org/10.1007/s10143-019-01097-1

25. Hampton MB, Kettle AJ, Winterbourn CC (1998) Inside the neutrophil phagosome: oxidants, myeloperoxidase, and bacterial killing. Blood 92:3007–3017

26. Hazama F, Hashimoto N (1987) An animal model of cerebral aneurysm: preliminary evidence. Stroke 18:1651–1656. https://doi.org/10.1161/STROKEAHA.114.008589

27. Hazama F, Hashimoto N (2006) Involvement of myeloperoxidase in the formation of intracranial aneurysms. Stroke 37:90

28. Hazama F, Hashimoto N (2007) Myeloperoxidase in the formation of intracranial aneurysms: preliminary evidence. Stroke 45:1474–1477. https://doi.org/10.1161/STROKEAHA.114.004956

29. Hazama F, Hashimoto N (2008) Involvement of myeloperoxidase in the formation of intracranial aneurysms: preliminary evidence. Stroke 39:382–387. https://doi.org/10.1161/STROKEAHA.114.004956

30. Hampton MB, Kettle AJ, Winterbourn CC (1998) Inside the neutrophil phagosome: oxidants, myeloperoxidase, and bacterial killing. Blood 92:3007–3017

31. Hazama F, Hashimoto N (1987) An animal model of cerebral aneurysms. Neuruphol Appl Neurobiol 13:77–90

32. Ingall T, Asplund K, Mahonen M, Bonita R (2000) A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke 31:1054–1061

33. Ingall T, Asplund K, Mahonen M, Bonita R (2000) A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke 31:1054–1061

34. Jamous MA, Nagahiro S, Kitazato KT, Tamura T, Aziz HA, Shono M, Satoh K (2007) Endothelial injury and inflammatory response...
induced by hemodynamic changes preceding intracranial aneurysm formation: a systematic study in rats. J Neurosurg 107:405–411. https://doi.org/10.3171/JNS080405
35. Jusko M, Potempa J, Karim AY, Ksiazek M, Riesbeck K, Garred P, Eick S, Blom AM (2012) A metalloproteinase kariyisin present in the majority of Tannerella forsythia isolates inhibits all pathways of the complement system. J Immunol 188:2338–2349. https://doi.org/10.4049/jimmunol.1101240
36. Kanematsu Y, Kanematsu M, Kurihara C, Tada Y, Tsou TL, van Rooijen N, Lawton MT, Young WL, Liang EI, Nuki Y, Hashimoto T (2011) Critical roles of macrophages in the formation of intracranial aneurysm. Stroke 42:173–178. https://doi.org/10.1161/STROKEAHA.110.590976
37. Kataoka K, Taneda M, Asai T, Kinoshita A, Ito M, Kuroda R (1999) Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. Stroke 30:1396–1401
38. Kinane DF, Stathopoulou PG, Papapanou PN (2017) Periodontal diseases. Nat Rev Dis Primers 3:17038. https://doi.org/10.1038/nrdp.2017.38
39. Korja M, Lehto H, Juvela S (2014) Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. Stroke 45:1958–1963. https://doi.org/10.1161/STROKEAHA.114.005318
40. Kosierkiewicz TA, Factor SM, Dickson DW (1994) Immunocytochemical studies of atherosclerotic lesions of cerebral berry aneurysms. J Neuropath Exp Neurol 53:399–406
41. Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry V, Kouznetsov E, Raymond J (2013) Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. J Neurol Neurosurg Psychiatry 84:42–48. https://doi.org/10.1136/jnnp-2011-302068
42. Kozarov EV, Dom BR, Shelburne CE, Dunn WA Jr, Progulske-Fox VA, Sahasrabudhe A, Dewhirst FE (2001) Bacterial diversity in human subgingival plaque. J Bacteriol 183:3770–3783. https://doi.org/10.1128/JB.183.12.3770-3783.2001
43. Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I (2004) Human atherosclerotic plaque contains viable invasive Porphyromonas gingivalis. Arterioscler Thromb Vasc Biol 25:17. https://doi.org/10.1161/01.ATV.0000155018.67835.1a
44. Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I (2004) Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 8:635–642. https://doi.org/10.1016/S1474-4422(09)70126-7
45. Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I (2004) Human atherosclerotic plaque contains viable invasive Porphyromonas gingivalis. J Immunol 181:5537–5542. https://doi.org/10.4049/jimmunol.1101240
46. Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I (2004) Human atherosclerotic plaque contains viable invasive Porphyromonas gingivalis. J Immunol 181:5537–5542. https://doi.org/10.4049/jimmunol.1101240
47. Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I (2004) Human atherosclerotic plaque contains viable invasive Porphyromonas gingivalis. J Immunol 181:5537–5542. https://doi.org/10.4049/jimmunol.1101240
48. Lundberg K, Wegner N, Yucel-Lindberg T, Venables PJ (2010) Periodontitis in RA-the citrullinated enolase connection. Nat Rev Rheumatol 6:727–730. https://doi.org/10.1038/nrrheum.2010.139
49. Malm S, Jusko M, Eick S, Potempa J, Riesbeck K, Blom AM (2012) Acquisition of complement inhibitor serine protease factor I and its co-factors C4b-binding protein and factor H by Prevotella intermedia. PLoS One 7:e34852. https://doi.org/10.1371/journal.pone.0034852
50. Miller DP, Bell JK, McDowell JV, Conrad DH, Burgner JW, Heroux A, Marconi RT (2012) Structure of factor H-binding protein B (FhB) of the periopathogen, Treponema denticola: insights into progression of periodontal disease. J Biol Chem 287:12715–12722. https://doi.org/10.1074/jbc.M111.339721
51. Naggara ON, Lecler A, Oppenheim C, Meder JF, Raymond J (2012) Endovascular treatment of intracranial unruptured aneurysms: a systematic review of the literature on safety with emphasis on subgroup analysis. Radiology 263:828–835. https://doi.org/10.1148/radiol.12112114
52. Nieuwkap DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ (2009) Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 8:635–642. https://doi.org/10.1016/S1474-4422(09)70126-7
53. Ollikainen E, Tulamo R, Frosen J, Lehti S, Honkanen P, Henssniemi J, Niemela M, Kovanen PT (2014) Mast cells, neo-vascularization, and microhemorrhages are associated with saccular intracranial artery aneurysm wall remodeling. J Neuropath Exp Neurol 73:855–864. https://doi.org/10.1097/NEN.0000000000000105
54. Ollikainen E, Tulamo R, Lehti S, Henssniemi J, Niemela M, Kovanen PT, Frosen J (2018) Myeloperoxidase associates with degenerative remodeling and rupture of the saccular intracranial aneurysm Wall. J Neuropath Exp Neurol 77:890–903. https://doi.org/10.1093/jnen/jny006
55. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, Deanfield J, D’Auito F (2014) Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. Atherosclerosis 236:39–46. https://doi.org/10.1016/j.atherosclerosis.2014.06.002
56. Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, Sahasrabudhe A, Dewhirst FE (2001) Bacterial diversity in human subgingival plaque. J Bacteriol 183:3770–3783. https://doi.org/10.1128/JB.183.12.3770-3783.2001
57. Popadiak K, Potempa J, Riesbeck K, Blom AM (2007) Biphasic effect of gingipains from Porphyromonas gingivalis on the human complement system. J Immunol 178:7242–7250
58. Popadiak K, Potempa J, Okroj M, Popadiak K, Eick S, Nguyen KA, Riesbeck K, Blom AM (2008) Binding of complement inhibitor C4b-binding protein contributes to serum resistance of Porphyromonas gingivalis. J Immunol 181:5537–5544
59. Popadiak K, Potempa J, Kanatyka T, Nguyen KA, Wawrzonek K, Manandhar SP, Popadiak K, Riesbeck K, Eick S, Blom AM (2009) Interpin A, a cytokine protease from Prevotella intermedia, inhibits complement by degrading complement factor C3. PLoS Pathog 5:e1000316. https://doi.org/10.1371/journal.ppat.1000316
60. Pussinen PJ, Althin J, Jousilahti P, Paju S, Tuomilehto J (2007) Systemic exposure to Porphyromonas gingivalis predicts incident stroke. Atherosclerosis 193:222–228
