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1 ***Porphyromonas*: a neglected potential key genus in human microbiomes**

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13

14

15 **Highlights**

- 16 • *Porphyromonas* is a bacterial genus that belongs to the respiratory core microbiome
- 17 • Important species in the pulmonary niche are *Porphyromonas* other than *P. gingivalis*
- 18 (POTG)
- 19 • POTG are understated and little studied
- 20 • The abundance of POTG is decreased whatever the respiratory disease
- 21 • POTG are also an interesting target of investigation in non-pulmonary microbiomes,
- 22 particularly gastric, oral and cutaneous.

23 **Abstract**

24 Anaerobes form a large part of microbial communities, and have begun to be specifically
25 studied in both healthy and pathologic contexts. *Porphyromonas* is one of the top ten anaerobic
26 taxa in the microbiome (anaerobiome) in healthy subjects. However, to date, most studies
27 focused on the deleterious role of *P. gingivalis*, the most widely described species. Interestingly,
28 targeted metagenomics reveals *Porphyromonas* other than *gingivalis* (POTG), highlighting other
29 species such as *P. catoniae* or *P. pasteri* as potential biomarkers in disease progression or
30 pathogen colonization susceptibility. From the sparse data, it appears that the *Porphyromonas*
31 genus may also be a relevant target of investigation in several pulmonary diseases. Moreover,
32 deciphering cutaneous, gastric and oral microbiomes hint that *Porphyromonas* may be a genus
33 of interest in non-pulmonary diseases.

34 This review aims to summarize the major data on POTG and to report their impact on the
35 various human microbiomes in different clinical states.

36

37 **Keywords**

38 *Porphyromonas*, *Porphyromonas catoniae*, *Porphyromonas pasteri*, anaerobes, lung
39 microbiome, skin microbiome, gastric microbiome, oral microbiome

40

1. Introduction

41 In recent years, new mass sequencing technologies have enabled description of
42 numerous communities of microorganisms, including unknown or overlooked microbial
43 populations, in almost all niches of the human body. These microbiomes are now well studied
44 and provide many keys to understand organ homeostasis and disease pathophysiology. An
45 iconic example is the gut microbiota, and its implication in obesity, Crohn's disease, autism and
46 many other diseases [1,2].

47 Focusing on strict anaerobes in the various human niches provides much information,
48 describing important genera or species as targets for scientific research. For instance, in
49 deciphering the gut microbiome, two important strict anaerobes, *Faecalibacterium prausnitzii*
50 and *Akkermansia muciniphila*, were discovered [3,4] and became the cornerstone in
51 understanding the pathophysiology of chronic inflammatory diseases and obesity. In the lung
52 microbiome, the importance of anaerobes is clear [5]. The lungs used to be considered a sterile
53 environment [6], but it is now known that healthy lungs host anaerobes [5] and that this
54 "anaerobiome" is resident in this ecological niche in healthy subjects [7–11]. Several anaerobe
55 genera are of particular interest, one of which is *Porphyromonas*. Many studies have focused on
56 *Porphyromonas gingivalis*; in contrast, little is known of *Porphyromonas* other than *gingivalis*
57 (POTG). Since the outset of microbiome studies, few data have been collected, most often
58 fortuitously, and are dispersed in the scientific literature, often as "supplementary information".
59 The present review, based on our previous results showing a potential role of *Porphyromonas*
60 *catoniae* in the lung microbiome of patients with cystic fibrosis (CF) [12,13], provides an

61 overview of anatomical sites where POTG have been reported, and describes their inherent
62 potential roles in human health and disease.

63

64 **2. Literature search and selection**

65 A systematic search for relevant literature published before October 31, 2019 was conducted in
66 PubMed, and Scopus. The following search terms were used to identify relevant articles:
67 ("*Porphyromonas catoniae*" OR "*Porphyromonas pasteri*" OR "*Porphyromonas*" NOT
68 "*gingivalis*"). One investigator (CAG) screened each abstract for inclusion, and two investigators
69 (CAG and GHA) were independently reviewed full texts. The references of the included articles
70 were studied to identify additional relevant articles. Any discrepancies between the authors
71 were resolved with two other investigators (CL and CB).

72 After initial screening, 840 articles in Pubmed and 91 in Scopus met our inclusion criteria. All but
73 80 articles identified in Scopus were also identified in PubMed, leaving a total of 851 unique
74 publications. There were 106 articles published before 2019 that were deemed relevant after
75 abstract review, and 39 articles that were excluded after full text review. An additional 22
76 articles were identified in the references of the included articles bringing the total number of
77 included articles published before 2019 to 89.

78

79 **3. The genus *Porphyromonas***

80 *Porphyromonas* is a Gram-negative, obligatorily anaerobic, non-spore-forming, non-motile
81 genus. In 2015, the number of validated species was 16 [14], but new species were more
82 recently described or are under description [15]. The type species among the genus is
83 *P. asaccharolytica* [14], and two classes of species can be distinguished according to their
84 natural reservoir. Some species were mainly isolated from human samples (*P. asaccharolytica*,
85 *P. endodontalis*, *P. gingivalis*, *P. catoniae*, *P. pasteri*, *P. somerae*, and *P. uenonis*), and at least 10
86 others mostly from animal samples (*P. cangingivalis*, *P. canoris*, *P. cansulsi*, *P. circumdentaria*, *P.*
87 *crevioricanis*, *P. gingivicanis*, *P. salivosa*, *P. macacae*, *P. gulae*, and *P. levii*) (Figure 1) [14,16].
88 Most species are black pigmented due to production of protoheme, with the exception of
89 *P. catoniae*, *P. bronchialis*, and *P. pasteri*. Major fermentation products comprise n-butyric acid
90 and acetic acid; propionic, isovaleric, isobutyric and phenylacetic acid may also be produced.
91 Hemin and vitamin K₁ are required to stimulate growth in most *Porphyromonas* species.
92 *Porphyromonas* is a slow-growing bacterium, as at least 48 hours' incubation at 37°C is
93 necessary for colony detection, and 7 days' incubation at least is recommended to improve
94 detection of all *Porphyromonas* species. *Porphyromonas* species are susceptible to most of the
95 antimicrobial agents recommended for anaerobic infection treatment: amoxicillin-clavulanate,
96 ampicillin-sulbactam, piperacillin-tazobactam, imipenem, cephalosporins and metronidazole. All
97 *Porphyromonas* species are susceptible to vancomycin, except *P. catoniae*. Natural resistance to
98 colistin, fosfomycin, polymyxin B and kanamycin was reported. Production of β-lactamase has
99 been reported in *P. asaccharolytica*, *P. catoniae*, *P. somerae* and *P. uenonis* [14,17]. The genus
100 was firstly, and is most often, reported in the oral cavity [18,19]. One of the major species in this
101 niche is *P. gingivalis*, which is a well-known and well-studied pathogen associated with

102 periodontitis [20]. *P. catoniae*, in contrast, was isolated mostly in control subjects [21–23]. The
103 genus *Porphyromonas* has been described in various other body sites including: lungs [11,24],
104 gut [25–27], skin [28,29], stomach [10,30], vagina [31] and nose [10,32].

105

106 **4. Lung microbiota**

107 The dogma of the sterile lung microbiome was discarded only recently [6], mainly thanks
108 to the application of metagenomics to lung samples [32]. Using independent culture methods,
109 lungs were shown to shelter anaerobes [7–11]. These findings were confirmed by extended
110 culture-based methods [24]. In the past, lung detection of anaerobes was associated with oral
111 contamination [33], but this has been widely disputed in recent years. It is now clear that
112 anaerobes are also lung residents [5,34].

113 At first sight, the presence of anaerobes in the lungs may seem surprising, but can easily
114 be explained by the presence of physiological gas gradients within the lung, independently of
115 whether the lung is healthy or not, enabling onset of a partial pressure gradient in oxygen and
116 carbon dioxide [35].

117 In this context, *Porphyromonas* was detected in the lung of healthy subjects, and
118 described as a member of the core microbiota [7–11]. It is one of the major anaerobic genera,
119 along with *Prevotella*, *Veillonella* and *Fusobacterium* [36]. The genus *Porphyromonas* appears
120 early in life and is detected in the lower airway microbiota before 1 year of age [37]. Pattaroni *et*
121 *al.* showed that the lower airway microbiota of neonate patients is a key determinant for

122 immune system maturation in the respiratory tract, and that the healthy pulmotype contains
123 multiple bacterial species, including *Porphyromonas* [37]. Presence of *Porphyromonas* in the
124 lungs was also noted in adults [8,10]. No differences were observed between smokers and non-
125 smokers in terms of relative abundance of *Porphyromonas* in lung [8,11]. Interestingly, based on
126 a twin family cohort, Lim *et al.* [11] highlighted that *Porphyromonas* is one of the heritable taxa
127 that are selected by genetic factors from the host.

128 Interestingly, microbiological continuity has been described in the aerodigestive tract in
129 healthy adults [10]. Microbial immigration from the oral cavity appears to be the primary source
130 of the healthy lung microbiome. Bacterial communities in the healthy lung overlapped with
131 those found in the mouth, but were found at lower concentrations, with different community
132 composition and less diversity [10]. Among the bacterial species shared between the oral cavity
133 and the lungs, many anaerobes were identified, including *Porphyromonas*.

134

135 **5. Cystic Fibrosis (CF)**

136 CF is an autosomal recessive genetic disease due to mutations on the *cftr* (cystic fibrosis
137 transmembrane conductance regulator) gene. These mutations affect the CFTR protein and
138 alter regulation of chloride ion and water transport across epithelial cells. One of the major
139 consequences of these mutated proteins is the development of hyperviscous mucus which,
140 combined with impaired immune response, weakens the endogenous lung microbiota to the
141 benefits of pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* or the
142 *Burkholderia cepacia* complex [5].

143 *Porphyromonas* was first detected by Rogers *et al.* [38], who used terminal restriction
144 fragment length polymorphism profiling to characterize bacterial community diversity in CF lung
145 infection. Since then, the genus was detected in many studies targeting CF populations, using
146 culture-independent methods as well as culturomics (also called extended culture methods,
147 based on the use of a high number of culture media and conditions) [24,39–42], and was
148 classified as a member of the core CF lung microbiome [39]. Culturomics provided proof of
149 viability of *Porphyromonas* isolated within the microbiota [43]. The main species detected were
150 *P. catoniae*, *P. endodontalis*, *P. levii*, *P. pasteri* and *P. uenonis* [13,38,39,42,44] and, in a lesser
151 proportion, *P. gingivalis* [45]. *P. catoniae*, *P. uenonis* and *P. pasteri* were revealed using bacterial
152 extended culture of airway samples, unlike *P. gingivalis* which has so far only been revealed by
153 metagenomics [24]. At this point, it is important to underline that *P. gingivalis* constitutes a
154 minority of the *Porphyromonas* species within the pulmonary microbiome, in contrast to the
155 oral microbiome.

156 In CF, children are rapidly colonized, before 1 year of age, by the genus *Porphyromonas*
157 [46], which is one of the top 10 taxa in terms of relative abundance in bronchoalveolar lavage

158 (BAL) in clinically well CF infants [41]. Prevalence peaks at 10-60% at the age of 13-17 years
159 [24,42] , then decreases with age [24,42]. After 45 years, another increase in several anaerobic
160 genera, including *Porphyromonas*, is observed [42]; in this group of patients, with less severe
161 disease phenotype (life expectancy of at least 45 years), *Porphyromonas* reaches almost the
162 same prevalence as in the 6-10 year-old group. According to Carmody *et al.* [42], this second
163 peak of anaerobic genera may be a survival effect linked with this extreme phenotype.

164 *Porphyromonas* lung colonization seems to be driven by different factors, and especially
165 host characteristics. Firstly, *Porphyromonas* is one of the bacterial genera in which variance is
166 explained by additive genetic effects, *i.e.* two or more genes or alleles contributing to its
167 presence in the lungs [11]. The underlying disease may also influence *Porphyromonas* level,
168 which is greater in non-CF than CF children [46]. In CF, there is a negative correlation between *P.*
169 *catoniae* and F508del mutation (the major *cftr* mutation) [47]. Moreover, the clinical status of
170 CF patients (e.g., *P. aeruginosa* colonization/infection) seems to influence *Porphyromonas*
171 [13,48]. Patient age is also a factor: a negative correlation was found between *P. catoniae* and
172 patient age [46,47]. Finally, environmental/exogenous factors may also have an impact on
173 *Porphyromonas* colonization; *Porphyromonas* abundance was higher in the nasopharyngeal
174 microbiota of a formula-fed than in a breast-fed group of CF infants [49].

175 Focusing on the ecological networking of CF lung infection, an interesting dynamic
176 between *Porphyromonas* and some important CF pathogens was established. Quinn *et al.* [48]
177 described a cluster of 17 operational taxonomic units (OTUs), including *Prevotella*, *Parvimonas*,
178 *Veillonella*, *Porphyromonas* and *Fusobacterium*, with positive interactions. Contrarily, a negative
179 correlation was observed between some commensal taxa (*Streptococcus*, *Porphyromonas* and

180 *Prevotella*) and *Pseudomonas* [13,48,50]. The hypothesis is that fermentative anaerobes are
181 able to create a micro-environment favorable to growth, while simultaneously making the
182 environment less suitable for *P. aeruginosa* [48]. The same trend was observed in
183 oropharyngeal samples, where *Porphyromonas* was the fourth genus in terms of relative
184 abundance to decrease over time prior to initial *P. aeruginosa* colonization [27]. Quinn *et al.*
185 [48] also found that *S. aureus* interacts negatively and exclusively with *Porphyromonas*. A recent
186 study combined methodological strategies, including the “change-point” method (association
187 between changes in key taxa abundance and changes in patient clinical status over time), to
188 identify key taxa during CF exacerbation [51]. *Porphyromonas* was the first genus in terms of
189 relative frequency to be modified during exacerbation, and among the top 10 genera modified
190 in the “unwell” clinical state, according to a method based on network interconnectedness. In
191 another study, *Porphyromonas* was positively associated with lung function measured by forced
192 expiratory volume (FEV-1), and increased after initiation of ivacaftor, a CFTR potentiator [12].
193 These results favor the hypothesis of an association between *Porphyromonas* and improved or
194 stable pulmonary state.

195 Looking more deeply into the taxonomic affiliation of *Porphyromonas*, *P. catoniae* appeared to
196 be of particular interest. Cuthberston *et al.* [40] investigated the resistance and resilience of
197 pulmonary microbiota to exacerbation and antimicrobial intervention. They found that
198 *P. catoniae* provided the greatest contribution to dissimilarities between disease periods
199 (baseline, exacerbation, treatment and recovery), with the exception of the comparison
200 between the treatment and recovery periods, where *Veillonella parvula* provided the largest
201 contribution [40]. Plotting *P. catoniae*'s relative abundance during the clinical stages of CF

202 disease, a drop between baseline and exacerbation and a significant drop during the treatment
203 phase were observed. In contrast, an increase in *P. catoniae* abundance was observed between
204 the treatment and recovery phases, with a final return to baseline. A recent study echoed this
205 finding, showing an inverse dynamic between *P. catoniae* and *P. aeruginosa* in CF patients
206 during early *P. aeruginosa* colonization [13]. Based on combined microbiome and targeted qPCR
207 approaches, this study found that patients depleted in *P. catoniae* were more susceptible to
208 colonization by *P. aeruginosa*. Moreover, the drop in *P. catoniae* abundance was found before
209 *P. aeruginosa* colonization. This longitudinal study thus supported the idea of *P. catoniae* as a
210 potential predictive biomarker of early *P. aeruginosa* colonization in CF patients [13].

211 The biological effects of the genus *Porphyromonas* and of *P. catoniae* in particular in the
212 CF airway remain to be deciphered. The keys to understanding may reside in the study of
213 *Porphyromonas* metabolites, including sphingolipids, fermentation-induced metabolites such as
214 short-chain fatty acids, and metabolites of quorum-sensing [5].

215

216 **6. Chronic Obstructive Pulmonary Disease (COPD)**

217 Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder with
218 irreversible obstruction of the respiratory tract, and is usually classified in severity stages from
219 mild to severe. The association of two factors causes this condition: reduced bronchiole caliber
220 and destruction of the pulmonary alveoli. *Porphyromonas* was described as a member of the
221 lung core microbiota in patients with COPD [7,52], but in decreased abundance as in CF patients
222 [53]. Some studies analyzed the airway microbiota to find markers of progression or better lung

223 function. In 2017, Engel *et al.* [54] investigated the correlation between lung computed
224 tomography (CT) changes and lung microbiome in patients with COPD, and found greater
225 abundance of *Porphyromonas* in the mild/healthy group than in the severe group.
226 *Porphyromonas* was present in a co-occurrence network also composed of *Tannerella* and
227 *Prevotella*. This study suggested that modifications in the microbial colonization of the lungs in
228 COPD patients occur early, before significant impairment of health status, with the possibility of
229 using bacterial biomarkers to characterize disease progression. Some studies assessed markers
230 of disease progression in investigating the lung microbiota. Sze *et al.* [55] investigated host
231 response to the lung microbiome in COPD, and highlighted 10 OTUs able to discriminate
232 controls from severe-stage COPD (GOLD 4). In these 10 OTUs, *Porphyromonas* was depleted in
233 COPD patients compared to controls. A study of pharyngeal samples by Diao *et al.* [52] found
234 that *P. endodontalis* and *P. catoniae* levels correlated with FEV-1. The authors investigated the
235 biomarker capacity of *P. endodontalis* (in combination with two other OTUs) in discriminating
236 COPD patients from controls; sensitivity was 71.1% and specificity 75.0%. Surprisingly, Lee *et al.*
237 [56] found contrasting results investigating the metagenome and metatranscriptome of
238 moderate and severe COPD sputum samples, with higher *Porphyromonas* levels in severe than
239 moderate COPD; however, the identified species were *P. gingivalis* and *P. asacharolytica*
240 (supplementary data), known as pathogens, whose main niche seems not to be in the lungs,
241 unlike for example *P. catoniae*. This observation highlighted the importance of taxonomic
242 affiliation at species level, which could be an issue in 16S metagenomics-based studies. Clinical
243 interpretation of bacterial genera frequently switches at species or even strain level, from a
244 beneficial to a pathogenic species, modifying the study's conclusions.

245 **7. Other pulmonary diseases**

246 *7.1 Lung cancer*

247 Lung cancer is another major chronic pulmonary disease associated with
248 *Porphyromonas*. Recent studies assessed the involvement of *P. gingivalis* in oral cancer and lung
249 metastasis [57]. Interestingly, studies that focused on the lower respiratory tract found a
250 positive role of *Porphyromonas*. Exploring both saliva and BAL samples from patients with
251 pulmonary bronchogenic carcinoma, Wang *et al.* [58] found that patients with pulmonary
252 cancer showed less microbial diversity than controls. The relative abundance of *Porphyromonas*
253 was lower in BAL samples from lung cancer patients, and *Porphyromonas* relative abundance
254 was higher in the microbiome of healthy subjects. These results are consistent with those of Yan
255 *et al.* [59] for potential bacterial biomarkers of lung cancer; using saliva samples, they found
256 that the relative abundance of *Porphyromonas* was significantly lower in patients with
257 squamous cell carcinoma, and also (but non-significantly) lower in patients with
258 adenocarcinoma. The recent study by Zhang *et al.* [60] also found significantly lower levels of
259 anaerobes, including *Porphyromonas*, in the saliva of non-small-cell lung cancer patients
260 compared to controls. Finally, a study by Han *et al.* [61], comparing the tongue microbiota of
261 healthy subjects versus lung, colorectal and gastric cancer patients, found higher relative
262 abundance of *Neisseria*, *Haemophilus*, *Fusobacterium*, and *Porphyromonas* in the healthy
263 controls. Although not all sample sites were in the lower airway microbiota, all these results
264 agree on a decrease in *Porphyromonas* levels (presumed to be POTG) in lung cancer.

265 *5.2 Tuberculosis*

266 *Porphyromonas* was also reported to be involved in the course of tuberculosis (TB) [62].
267 Comparing BAL samples between patients with TB and healthy subjects, the abundance of
268 *Mycobacteria* and *Porphyromonas* was significantly higher in TB pulmonary lesions than in non-
269 lesion areas in the contralateral lung; But comparing the top 30 genera in terms of abundance in
270 each condition (healthy, TB lung without lesion, TB lung with lesion), *Porphyromonas* levels
271 were lower in TB lungs without lesion than in controls, and no longer in the top 30 genera.

272 **8. *Porphyromonas* in non-pulmonary pathologies**

273 *6.1 Rheumatoid arthritis*

274 *Porphyromonas* was detected in BAL samples from rheumatoid arthritis (RA) patients
275 [63]. RA is a complex multifactorial disease, the etiology of which is not well explained. Recently,
276 the role of periodontal disease, especially driven by *P. gingivalis*, was highlighted [64]. In this
277 context, Scher *et al.* investigated the lung microbiota in BAL samples in early RA and sarcoidosis
278 [63]. Contrary to their initial hypothesis, only 10% of patients with RA were colonized by
279 *Porphyromonas*, versus 40% of controls. The relative abundance of both *Porphyromonadaceae*
280 and *Porphyromonas* was significantly lower in patients with RA or sarcoidosis. Thus, despite the
281 fact that *P. gingivalis* is an important pejorative actor in RA, the relative abundance of
282 *Porphyromonas* in the lungs seems to be decreased in disease, again highlighting the fact that
283 *Porphyromonas* lung species (which may be POTG) may not have the same action as *P.*
284 *gingivalis*.

285 *6.2 Sjögren's syndrome*

286 A change in *Porphyromonas* abundance has also been observed in Sjögren's syndrome. A
287 decrease in the relative abundance of *Porphyromonas* was observed in oral rinse fluid or saliva
288 in patients with Sjögren's syndrome [65–67].

289 Looking at the species level, Rusthen *et al.* identified *P. pasteri* as the one with significantly
290 lower prevalence in patients with primary Sjögren's syndrome than in controls (26.7% vs 80%)
291 [67].

292

293 6.3 Oral diseases

294 Studies investigating the oral microbiome in periodontitis compared to healthy controls
295 also found this contrast between *P. gingivalis* and POTG. *P. catoniae* was reported to be a
296 member of the healthy oral microbiome, and *P. gingivalis* as a member of the core microbiome
297 in case of periodontitis [20–23].

298 In the context of oral squamous cell carcinoma, *Porphyromonas* quantified in oral rinsing
299 has been identified as being decreased (with *Streptococcus*, *Haemophilus* and *Actinomyces*)
300 during cancer progression [68]. This result has been proven by a single author and needs to be
301 confirmed, as well as the species involved need to be specified. When analyzed up to the
302 species level, *P. pasteri* was inversely associated with the progression of oral squamous cell
303 carcinoma, and was selected by the authors as a member of a bacterial panel to distinguish
304 patients with oral squamous cell carcinoma (stages 2, 3 and 4) from healthy individuals.

305 6.4 Skin diseases

306 *Porphyromonas* was described within the skin microbiota. *Porphyromonas* was detected
307 on the skin of healthy subjects, and even in infants less than 1 year old, but also in patients with
308 atopic dermatitis [28,29]. Within this microbiome as well, *Porphyromonas* showed an
309 interesting contrast between healthy subjects and patients, and is one of the bacterial genera
310 than could be relevant biomarkers to discriminate between healthy skin and atopic dermatitis
311 and diagnose disease progression, either in combination with *Neisseria*, *Paenibacillus*,
312 *Granucateella* and *Enhydrobacter* [28], or with *Veillonella*, *Prevotella*, *Leptotrichia* and
313 *Agrobacterium* [29]. *Porphyromonas* levels were found to be decreased according to disease
314 status (mild, moderate and severe disease) with a significant difference between the healthy
315 and severe groups [29]. After treatment of atopic dermatitis, *Porphyromonas* abundance
316 increased. Conversely, *P. aeruginosa* abundance was increased in dermatitis [28]; these findings
317 echo those found in the CF lung microbiota, with a potential inverse correlation between
318 *Porphyromonas* and *P. aeruginosa* [13]. A study of systemic antibiotic treatment for acne
319 showed that antibiotic administration was associated with an initial decrease in bacterial
320 diversity, followed by recovery. The same pattern was observed for *Porphyromonas*, with a
321 significant drop in relative abundance at the start of antibiotic treatment and recovery after 12
322 weeks. In addition, a converse pattern was observed for *Pseudomonas* species, with a significant
323 rise in relative abundance on initiation of treatment and a return to baseline after 12 weeks
324 [69].

325 *6.5 Gastrointestinal diseases*

326 *Porphyromonas* was reported in gastric cancer. Comparing gastric microbiota composition
327 between non-atrophic gastritis and patients with intestinal gastric cancer, Aviles-Jimenez *et al.*

328 [30] reported lower abundance of *Porphyromonas* in patients with cancer than in patients with
329 gastritis. Two *Porphyromonas* OTUs were found, and were both significantly lower in the cancer
330 group. An interesting point is the predominance of *Pseudomonas* in patients with gastric cancer,
331 like in atopic dermatitis or CF lung disease. These results raise the question of a specific
332 interaction between *Porphyromonas* species and *Pseudomonas aeruginosa*, whatever the niche.
333 These findings were strengthened by a recent study by Kageyama *et al.* [70] investigating the
334 salivary microbiome in patients with various forms of digestive tract cancer (tongue, pharynx,
335 esophagus, stomach, and large intestine). They highlighted the importance of *P. gingivalis*,
336 which was more abundant in the saliva of all groups of cancer patients compared to control
337 subjects. The duality in *Porphyromonas* species was supported by a linear discriminant analysis
338 (LDA), *P. gingivalis* being more abundant in cancer patients while three other *Porphyromonas*
339 species, including *P. pasteri* (closely related to *P. catoniae*), were more abundant in control
340 subjects.

341 *Porphyromonas* was also described in the digestive tract, represented by two main species:
342 *P. asaccharolytica* [71,72] and *P. gingivalis* [73]. In healthy subjects, *Porphyromonas* was
343 exclusively detected in the distal mucosa, with a high range of relative abundance (0.01%-16%),
344 and consisting of the species *P. asaccharolytica* [71]. *Porphyromonas* was elevated in the
345 digestive tract of patients with colorectal cancer [72,74–77]. Conversely, several studies on oral
346 microbiota-derived biomarkers for gastrointestinal cancers highlighted a higher abundance of
347 *Porphyromonas* in controls' saliva and tongue coating compared to patients with colorectal
348 cancer, gastric cancer or pancreatic cancer [78–81]. A significant association was observed
349 between *P. gingivalis* and polyp location, with elevated abundance in case of proximal polyp

350 [76]. A significant positive association between polyp size and the absolute quantity of
351 *P. gingivalis* was also described [76]. A set of several bacteria, including *P. gingivalis* and *P.*
352 *asaccharolytica*, was significantly associated with colorectal cancer, and proposed as novel
353 biomarkers for early detection of adenomatous polyps and colon cancer [75,82].

354 6.6 Vaginal diseases

355 *Porphyromonas* was described as a member of the healthy vaginal microbiota [83], but was
356 mainly reported in a context of dysbiosis [31,84–86]. In vaginosis, the incriminated species was
357 *P. asaccharolytica* [31,84–86], which was positively associated with vaginosis and preterm
358 delivery [85]. *P. levii* [31], *P. somerae* [87] and *P. crevioricanis* [87] were also incriminated.
359 Higher prevalence of *P. gingivalis* was highlighted by molecular detection in chronic villous
360 tissue of women with unexplained recurrent early miscarriages [88]. Finally, *P. somerae* was
361 positively associated with endometrial cancer (in combination with *Atopobium vaginae*),
362 especially in case of vaginal pH >4.5 [87].

363 6.7 Human immunodeficiency virus (HIV) infection

364 A study of Li *et al.* [89] was conducted in HIV seronegative and HIV seropositive patients and
365 analyzed saliva microbiota from them using microarray. They highlighted that only seven genera
366 were detected in HIV negative samples, and *Porphyromonas* was among them. *Porphyromonas*
367 was detected in control subjects, not detected in HIV positive subjects before treatment, but
368 detected in HIV positive patients after treatment. Among the genus *Porphyromonas*, detected
369 species included *P. catoniae*, *P. endodontalis* and *P. gingivalis*.

370 **9. Conclusions**

371 In recent years, many studies of human microbiomes aimed to find potential probiotics
372 and biomarkers related to specific diseases. The lung “anaerobiome” has increasingly been of
373 interest and is now studied in CF and other chronic inflammatory lung diseases such as COPD.
374 Whatever the clinical context, disease and niche, *Porphyromonas* may become an important
375 genus to analyze in order to discriminate disease stage/progression and to predict pathogen
376 colonization. In line with this view of the implementation of the microbiome in precision
377 medicine, identification to species level is mandatory as there is a strong duality in
378 *Porphyromonas* between *P. gingivalis*, a pathogenic species, and some POTGs that are
379 potentially beneficial. To perform this, new strategies can be used, such as long reads
380 sequencing or even the use of extended culture, which is a reliable solution for the
381 identification of species or strains. Thus, it is important to discriminate between species and to
382 know exactly which are involved when discussing about *Porphyromonas*.

383 Few studies described POTG, but they all revealed a potential role for this group of
384 species in both pulmonary and non-pulmonary diseases. Many studies have implicated
385 *P. gingivalis* as a pathogen; However, it appeared that POTGs may have a different, even
386 beneficial, role.

387 Unfortunately, only a few studies described *Porphyromonas* at species level in
388 microbiomes; Consequently, the diversity of *Porphyromonas* species is understated. The
389 development of high-throughput culture methods, including anaerobic cultures, may improve
390 the description of this genus.

391 *Porphyromonas* should not be understated in *a priori* highly oxygenated microbiome,
392 such as the pulmonary or cutaneous microbiome. Anaerobic culture should be much more
393 systematically applied regardless of the site of origin of the sample.

394 In the future, POTGs could become new targets, to investigate their potential as
395 biomarkers of disease progression or pathogen colonization: e.g., *P. catoniae* and *P. aeruginosa*
396 in CF. Only prospective longitudinal cohort studies will answer these questions accurately.

397

398 **List of abbreviations**

399 BAL: Bronchoalveolar lavage

400 CF: Cystic fibrosis

401 COPD: Chronic obstructive pulmonary disease

402 CT: Computed tomography

403 FEV-1: Forced expiratory volume

404 GOLD: Global initiative for obstructive lung disease

405 LDA: Linear discriminant analysis

406 OTU: Operational taxonomic unit

407 POTG: *Porphyromonas* other than *P. gingivalis*

408 RA: Rheumatoid arthritis

409 TB: Tuberculosis

410 **Declaration of competing interest**

411 All authors report no conflict of interest.

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726 **Figure**

727 **Figure 1.** Unrooted tree showing the phylogenetic position of *Porphyromonas* species based on 16S
728 rRNA gene sequencing. The tree was performed with maximum parsimony method and MUSCLE MEGA,
729 using 1000 bootstraps replicates. (H), mainly described in humans; (A), mainly described in
730 animals.

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