

1 Review

2 Bacterial sialoglycosidases in virulence and 3 pathogenesis

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12

13 **Abstract:** Periodontitis is a chronic inflammatory disease affecting the tissues that surround and
14 support the teeth. In the U. S., approximately 65 million people are affected by this condition. Its
15 occurrence is also associated with many important systemic diseases such as cardiovascular disease,
16 rheumatoid arthritis, and Alzheimer's disease. Among the most important etiologies of
17 periodontitis is *Porphyromonas gingivalis*, a keystone bacterial pathogen. Keystone pathogens can
18 orchestrate inflammatory disease by remodeling a normally benign microbiota causing imbalance
19 between normal and pathogenic microbiota (dysbiosis). The important characteristics of *P. gingivalis*
20 causing dysbiosis are its virulence factors that cause effective subversion of host defenses to its
21 advantage [1], allowing other pathogens to grow. However, the mechanisms involving these
22 processes are poorly understood. However, various microbial strategies target host
23 sialoglycoproteins for immune dysregulation. In addition, the enzymes that break down
24 sialoglycoproteins/sialoglycans are the "sialoglycoproteases", resulting in exposed terminal sialic
25 acid. This process could lead to pathogen-toll like receptor (TLR) interactions mediated through
26 sialic acid receptor-ligand mechanisms. By assessing the function of *P. gingivalis*
27 sialoglycoproteases, could pave the way to designing carbohydrate analogues and sialic acid
28 mimetics to serve as drug targets.

29 **Keywords:** Sialidase, sialic acid, sialoglycoprotease, pathogenicity, therapeutic target, Siglec

30

31 1. Introduction

32 Human microbiota consists of about 100 trillion microbial cell that constantly interact with the
33 host counterpart through various mechanisms [2]. There exists a symbiotic relationship among these
34 microorganisms, however, such a state can be reverted to exploiting pathogenic potential by certain
35 organisms that lead to dysbiotic microbiota. Dysbiosis can lead to major pathogenic conditions
36 especially in the gut, oral and vaginal niche due to the richness of glycans that act as an energy source
37 to the microorganisms. Among the host pathogen interaction strategies, many microorganisms,
38 especially bacteria possess a strong affinity to sialic acid which coat the cell surface. Sialic acid has
39 been predominantly found as the terminal carbohydrate in eukaryotes and prokaryotes. Sialic acid
40 naturally occurs in prokaryotes as nine-carbon keto sugar acids derived from N-acetylneuraminic
41 acid (Neu5Ac) [3].

42

43 The major enzyme that facilitate this interaction between the host and pathogen is bacterial
44 "sialoglycosidases" – the enzymes which cleave the sialic acid from sialoglycoproteins. This include
45 the sialidases and sialoglycoproteases. Sialidases (neuraminidases) are glycosylhydrolases that

46 cleave the sialic acid (Sia) O-acceptor substrates by an exohydrolytic reaction. Functionally similar to
47 sialidases, the O-sialoglycoprotease hydrolyzes the Sia O-acceptor substrate through an
48 endohydrolytic reaction [4,5]. Sialidase activity has been found in viruses, bacteria, protozoa, fungi,
49 and metazoans [5–7]. Bacterial sialidases have been considered virulence factors in many pathogenic
50 organisms, such as *Corynebacterium diphtheriae*, *Vibrio cholerae*, *Streptococcus pneumoniae*, and group B
51 streptococci, which colonize mucosal surfaces [8]. They have been shown to be involved in infection
52 and tissue destruction [9], peroxide scavenging during oxidative stress [10], and the modulation of
53 host innate immunity [5]. Furthermore, production of sialoglycosidases may be a critical factor in the
54 provision of free sialic acid, a fermentable carbohydrate source for bacterial proliferation [8,11]. There
55 are four mammalian sialidases such as NEU1, NEU2, NEU3 and NEU4 and they are found in
56 lysosomes, cytosol, plasma membrane and lysosomes or mitochondria or endoplasmic reticulum
57 respectively [12].

58
59 The human oral microbiome is one of the major microbiota contributing to the overall
60 microbiome in humans. With more than 700 species of bacteria with varied diversifications in their
61 composition give a significant curiosity to study its role in both the oral and overall health of the
62 individual. Periodontitis is a general infectious disease affecting most of the population [13]. Many
63 commensal and pathogenic bacteria use environmental (host) sialic acids as sources of carbon,
64 nitrogen, energy, and amino sugars for cell wall synthesis [14]. The breakdown of sialic acid residues
65 and sialoconjugates by sialidases contributes to a wide range of important biological functions such
66 as cellular interaction and conformational stabilization of glycoproteins in the cell membrane that
67 could expose or mask receptors for ligand binding and other enzymatic interactions [15]. While the
68 role of sialidase in sialic acid metabolism has been known in other oral pathogens like *Tannerella*
69 *forsythia* [16], it is yet to be explored in *P. gingivalis*.

70 1.1. Sialic acid

71 Sialic acid is a derivative of neuraminic acid, a monosaccharide with nine carbon acidic sugar.
72 Sialic acids are present at the terminal location of the glycans of glycolipids, polysaccharides and
73 glycoproteins in the cell [17]. There are about 50 types of Sia but Neuraminic acid (Neu), N-
74 glycolylneuraminic acid (Neu5Gc), N - acetylneuraminic acids (Neu5Ac) and deaminated
75 neuraminic acid (KDN) are the four types of sialic acids which are the most frequent monosaccharides
76 [17,18]. These four dominant sialic acids are subjected to variety of modifications such as substitution
77 at, O -acetyl, O - sulfate, O - methyl, hydroxyl groups and phosphate groups [17]. Sialic acid are
78 detected on the other surface of cell such as terminal components of glycoprotein and glycolipids and
79 in cellular secretion of both eukaryotic and prokaryotic species [18].

80
81 A typical cell displays millions of Sialic acid molecules [19]. Given their ubiquitous presence and
82 abundance at the surface of all cell types (including those of the immune system), Sialic acids have
83 major biophysical effects. Earlier studies showed removal of Sialic acid from immune cell surfaces
84 using sialidases showed marked changes in behavior of such cells [20]. Removal of cell surface Sialic
85 acids has many potentially pleiotropic effects, such as, removal reduces the net charge and
86 hydrophilicity of the cell surface. It can reduce the charge repulsion between adjacent cell surface
87 molecules. It eliminates ligands for endogenous receptors like Siglecs and selectins (see below).
88 Sialic acid removal exposes underlying glycans (mostly galactose residues), which can be recognized
89 by other endogenous receptors, such as galectins and the galactose-binding proteins of macrophages
90 and receptors in the neutrophils.

91 1.2. Sialidase

92 Sialidase (neuraminidases) are superfamily of N-acylneuraminidase residues from the glycans
93 of polysaccharides, glycoproteins and glycolipids that are released by glycosyl hydrolases [17].
94 Sialidases are found in higher eukaryotes and in some pathogenic bacteria, viruses, fungi, metazoan
95 and protozoans. Structurally, sialidase can be divided into two types such as small and large based

96 on the difference in molecular mass and a differential calcium requirement for protein stability or
97 catalysis of some large sialidases [5]. The sialidases breaks down the residues of sialic acid and
98 sialoglycoproteins that could mask or expose that receptors for enzymatic interactions and ligand
99 binding by contributing to biological functions such as cellular interaction and conformational
100 stabilization of glycoproteins in the cell membranes [15].
101

102 All eukaryotes and prokaryotes exhibiting sialic acid produces sialidases but with different
103 substrate specificities. The cleavage of sialic acid from a substrate is specific to each different sialidase.
104 It is relied upon three important specialization that allow the eukaryotes to control their
105 sialoglycoconjugates turnover. They are (i) kind of kitosidic linkage, (ii) the nature of penultimate
106 sugar residues and (iii) the type of neuraminic acid derivation [21]. But in the case of prokaryotes, the
107 above factors does not correlates with the phylogenetic relationship [1].

108 2. Oral sialidase

109 In prokaryotes, over 70 different micro-organisms has been reported with sialidase activity [21].
110 When bacterial sialidases comes in contact with mammalian host, they become commensals or
111 pathogenic [17]. During the protein secretion process, the secretory proteins which are bacterial
112 sialidases containing single peptides are cleaved [2]. The optimum pH for the monomeric bacterial
113 sialidases is between 5 – 7 and their molecular weight ranges from 40 – 150 KDa [17,19,20,22]. Oral
114 bacteria that expresses sialidases degrades sialoglycoprotein substrates. They use sialic acid as sugars
115 to improve its growth [23]. Oral viridans Streptococci inclusive of *Streptococcus oralis*, *S.intermedine*,
116 *S.pneumoniae* and *S. mitis* strains produces sialidases [24,25]. In case of Streptococcus strains, sialic
117 acid (Neu5Ac) is mostly used as a source for carbon [25]. Most notable red complex organism
118 *Tannerella forsythia* exhibit sialidase dependent growth in biofilm and also produces inhibitors that
119 might be used as adjuncts in periodontal therapy [26]. Sialidases play a pivotal role in the virulence
120 and pathogenesis of the bacteria owing to their microenvironment rich in mucin and other
121 sialoglycoprotein rich environment such as the saliva. Certain bacteria has gene machinery that are
122 involved in metabolism of sialic acid however, some other bacteria do resort to alternative pathway
123 of sialic acid metabolism.

124 3. *Porphyromonas gingivalis* sialidase

125 *Porphyromonas gingivalis* is a non-motile, asaccharolytic, Gram – negative anaerobes that plays a
126 vital role in chronic periodontitis [27]. This bacterium mostly depends upon the energy produced by
127 the aminioacids fermentation to survive in periodontal pockets [28]. It is proved from studies that *P.*
128 *gingivalis* is associated with certain major systemic diseases such as cardiovascular disease, preterm
129 birth and diabetes [29].
130

131 According to Wilson Aruni et al, 2011 [30], it was identified that three sialidases related genes in
132 *P. gingivalis* has shown a specific pattern of clustering with other associated genes from the bacteria.
133 Enzymes such as sialidase and sialoglycoprotease are the key factor to satisfy the asaccharolytic
134 requirements of *P. gingivalis* by breaking down the glycoprotein conjugate, role of these enzyme in
135 sialic acid metabolism and its involvement in protein stability inclusive of gingipains. Hence it is
136 believed that the absence or presence of silaic acid modulates the important proteins that are involved
137 in both pathogenicity and metabolic of an organisms. It also implied that synergy between sialidases
138 and sialoglycoproteases are required by *P. gingivalis* to colonize the periodontal pockets [30].
139

140 Parker, D., et al. 2009 [31], Roy, S., et al 2010 [16] and Soong, G., et al. 2006 [32] studies have
141 proved that several bacteria including *Tannerella forsythia* exhibit biofilm production. But in case of
142 *P. gingivalis*, the invasion rates were significantly higher than the wild type compared to the mutant.
143 Hence, the role of sialidases and sialoglycoproteases are unclear in *P. gingivalis*. While the role of
144 sialidases in other oral pathogens are known, the role of *P. gingivalis*'s sialoglycosidases in virulence
145 modulation and pathogenesis is yet to be explored [30].

146 4. Immune evasion and host sialic acid interaction in pathogenesis

147 Sialidases is one of many hydrolase which is related with the host bacterial invasion. The initial
148 step in sialo – glycol – conjugate degradation starts with the action of sialidases due to the non –
149 reducing terminal position of sialic acid residues in oligosaccharides [8].

150
151 Sialic acid metabolism by bacteria starts by secreting a large amount of sialidases with high
152 specific activity which is inducible [33,34]. This role is associated to both pathogenic and nutritional
153 roles performed by the bacterial sialidases [35]. Sialic acid permease is a specific transporter for sialic
154 acid which utilizes carbon source as an energy to transport sialic acid for degradation of cellular sialic
155 acid [36–39]. This degradation is attained by the action of sialidases on sialo – glycoprotein releasing
156 sialic acid (Neu5Ac) through the sialic acid permease leading to degradation of Neu5Ac to N –
157 acetylmannosamine (ManNAc) by an enzyme called acylneuraminate puruvate lyase. This enzyme
158 is induced by sialic acid and it is cell bound [1,38,40]. The end point N – acetylmannosamine
159 (ManNAc) is apparently the central intermediate as it can be either used or broken down in the
160 biosynthesis of sialic acid [41]. The activity of sialidases is closely associated with the essential needs
161 for the metabolism of an bacteria [5,36,37,42].

162
163 Bacterial sialidases are considered to be virulence factors that aids in invasion and also spread
164 of the micro – organism into the host [22,40]. The silaidase have direct toxic effect to the host tissues
165 and other defensive metabolism [8].

166
167 Thus the general characteristics of sialidases and sialic acid metabolism in immune evasion and
168 host – pathogenesis are as follows [8]

- 169 • Large amount of extracellular enzymes with high specific activity.
- 170 • Inducible activity at the site of infection.
- 171 • Specificity of substrate shown at the site of colonization.

172 5. Siglecs

173 Siglecs are sialic acid binding Immunoglobulin (Ig) like lectins. They are the proteins that are
174 present on the cells of the immune system that helps in binding sialic acid [43,44]. Based on their
175 similarity in sequence, siglecs is divided into two subsets. Sialoadhesin (CD169; Siglec 1); CD22
176 (Siglec 2); Myelin – associated glycoprotein (MAG; Siglec 4) and Siglec 15 are distantly related by ~25
177 – 30 % sequence identity. Whereas, CD33 (Siglec 3) is the main subset of siglec that is ~50 – 99%
178 sequence identity, is progressing promptly among mammalian species [45,46]. Immunoreceptor
179 tyrosine – based inhibitory motifs (ITIMs) is one of the signaling motifs based on tyrosine that are
180 present in siglecs are involved in cell signaling and siglec endocytosis [47].

181
182 Several siglecs that interact with specific sialic acid modifications are expressed in human pathogens.
183 Mostly siglec – dependent recognition of human pathogen glycans leads to either advantage or
184 detriment of pathogen that can alter the immune responses [45]. Phagocytosis could feasibly be
185 inhibited by structural modifications of TLRs, PRRs and complement) lead to various immune
186 signaling events in neutrophils. This process establishes chronic periodontitis due to a transition from
187 microbial homeostasis to dysbiosis [92]. One of the immune mediators involved in such host
188 inhibitory signaling is Siglec-9. Siglec-9 interaction with sialophorin (CD43) a surface
189 sialoglycoprotein is selectively expressed on limpho-hemopoietic cells [93]. *P. gingivalis*
190 sialoglycoproteases expose sialic acid and modify sialoglycans on *P. gingivalis* virulence factors
191 causing the following effects: (i) the exposed sialic acid interacts with siglec-9 via the sialic acid
192 binding ligand (sialophorin– CD43), attenuating the host inflammatory signaling in neutrophils, and
193 (ii) the modified sialoglycans evade siglec- 1-mediated phagocytosis because of a change in

194 conformation, masking the sialic acid, and preventing siglec-1 interaction.

195

196 6. Sialic acid siglec interactions

197 Innate immunity is the first line of body defense that consists of cellular and humoral immune
198 components. Siglec acts as a negative regulator in immune cells by inhibiting the immensity of
199 immune responses [47–49]. Normally, human lack N- glycolylneuraminic acid (Neu5Gc) because of
200 the Cytidine monophosphate – N –acetylneuraminic acid (CMAH) gene mutation; which encodes for
201 the enzyme that is needed to convert Neu5Ac to Neu5Gc [50]. Siglec (sialic acid binding
202 Immunoglobulin (Ig) like lectin) are greatly influenced by sialic acid as it binds to sialylated glycan.
203 The resulting glycolipids and glycoprotein have the prospective to function for siglecs and other
204 glycan – binding protein as counter receptors [51].

205 7. *P. gingivalis* sialoglycosidases

206 7.1. *P. gingivalis* and dysbiosis

207 *P. gingivalis* is an important keystone periodontal pathogen also implicated in systemic
208 infections [15,34]. This anaerobic bacteria interferes with host immunity, enabling the emergence of
209 dysbiotic communities [5,15]. *P. gingivalis* causes dysbiosis by subverting host defenses to its
210 advantage [1], but the mechanisms leading to dysbiosis are poorly understood. Polymorphonuclear
211 leukocytes (neutrophils) represent the primary cellular defense system in healthy oral tissues [19].
212 Neutrophils are the most common leukocytes recruited to the periodontal pocket and are needed for
213 tissue homeostasis [35]. Recent studies indicate that neutrophils can assist the initiation and
214 progression of periodontitis when their function is subverted by periodontal bacteria [20]. Hence,
215 neutrophil-*P. gingivalis* interactions and subversion of innate immunity are key contributing factors
216 to the pathogenesis of periodontal disease.

217 7.2. Mechanisms of neutrophil subversion and gap

218 To date, most studies on *P. gingivalis* neutrophil subversion have focused on integrins and
219 complement mediated processes [1]. Both hypo- and hyper-recruitment of neutrophils can occur due
220 to deficiencies in the expression of β 2 integrin or their negative regulators, respectively; either
221 scenario causes unwarranted IL-17-dependent inflammatory bone loss. Moreover, microbial
222 hijacking of C5aR (CD88) signaling in neutrophils impairs neutrophil antimicrobial function while
223 promoting destructive inflammatory responses [20,35]. While neutrophil homeostasis plays an
224 important role in periodontitis, the role of sialic acid mediated mechanisms causing neutrophil
225 subversion has not been studied in *P. gingivalis*. A variety of important siglec (sialic acid recognizing
226 immunoglobulin-like receptor) interactions with bacterial, viral and protozoan pathogens are
227 beginning to be recognized. Recent research has shown that pathogenic group B *Streptococci* (GBS)
228 bind to these siglecs in a sialic acid-dependent fashion to downregulate leukocyte bactericidal
229 capacity [36].

230 7.3. Sialic acid interactions in virulence and immune interactions

231 Though earlier studies on many human commensal bacteria focused on the role of sialic acid as
232 a growth factor or carbon source, its unique role in virulence and immune subversion is yet to be
233 explored. *P. gingivalis* relies on interactions with the host sialoglycoproteins to mediate several
234 virulence and pathogenesis factors, including adhesion, internalization and manipulation of innate
235 and adaptive immunity [37]. Because the breakdown of sialoglycoproteins/sialoglycans exposes
236 terminal sialic acid. The mechanism of immune regulation through sialic acid interactions in *P.*
237 *gingivalis* has not been explored.

238

239 7.4. *P. gingivalis* sialoglycoproteases

240 A number of bacterial proteases have been associated with virulence; sialoglycoproteases are
241 unique and ubiquitous in the bacterial kingdom, and have been studied in the context of virulence to
242 some extent. However, they have not been studied for their role in immune modulation. The
243 periodontal pocket is a rich source of sialoglycoproteins, which are found in saliva and gingival
244 crevicular fluid [38]. The enzyme “sialoglycoproteases” expose sialic acid by breaking down
245 sialoglycoproteins [24–29]. Among the red complex bacteria, only the *P. gingivalis* genome codes for
246 two sialoglycoprotease genes. The role of oral bacterial sialoglycoproteases in host – pathogen
247 interactions has not been explored. Among the few other groups that study sialic acid function, we
248 are the only group to study *P. gingivalis* sialoglycoproteases and have the lead in this area.

249 7.5. Sialic acid specific interactions in neutrophils

250 Phagocytosis could feasibly be inhibited by structural modifications of TLRs, PRRs and
251 complement) lead to various immune signaling events in neutrophils. This process establishes
252 chronic infection due to a transition from microbial homeostasis to dysbiosis [52]. One of the immune
253 mediators involved in such host inhibitory signaling is Siglec-9. Siglec-9 interaction with sialophorin
254 (CD43) a surface sialoglycoprotein which is selectively expressed on lympho-hemopoietic cells [53].
255 One of our study hypothesize that *P. gingivalis* sialoglycoproteases both expose sialic acid and modify
256 sialoglycans on *P. gingivalis* virulence factors causing the following effects: (i) the exposed sialic acid
257 interacts with siglec-9 via the sialic acid binding ligand (sialophorin– CD43), attenuating the host
258 inflammatory signaling in neutrophils, and (ii) the modified sialoglycans evade siglec- 1-mediated
259 phagocytosis because of a change in conformation, masking the sialic acid, and preventing siglec-1
260 interaction.

261 7.6. *P. gingivalis* sialoglycoproteases in virulence modulation

262 Most interactions between bacterial pathogens and their hosts are influenced by the pattern of
263 expressed glycans and glycan-binding receptors (lectins/adhesins/agglutinins) [36]. Several
264 medically important bacterial pathogens display sialic acid on their surface as an anti-recognition
265 molecule; this allows bacteria to masquerade as “self” and thereby elude or subvert host immune
266 responses. Exploring the mechanisms by which sialylated pathogens exploit host receptor systems to
267 modulate virulence is novel and new. We have identified unique sialoglycans on the surface of *P.*
268 *gingivalis* wild type (W83) cell surface that were missing in PG-Sgps isogenic mutants. Capsular
269 polysaccharides of pathogenic bacteria such as Group B *Streptococci* display sialoglycan structures
270 that both resemble vertebrate glycoproteins and can bind to siglecs on leukocytes [39]. Our
271 preliminary data showed that *P. gingivalis* exhibits similar sialoglycan structure, with sialic acid
272 linkages [31]. Also, certain siglecs such as siglec-9 on neutrophils bind to host α 2,3 linked sialic acid,
273 causing inhibitory signals. We have shown that *P. gingivalis* interacts with α 2,3- and α 2,6-linked sialic
274 acid moieties in human cells. The capsular glycan of *P. gingivalis* can elicit the inflammatory cytokines
275 MIP-2, RANTES and MCP-1 in murine macrophages. This suggests that the interactions in both
276 neutrophil adhesion and host inhibitory signaling, which are two key mechanisms utilized by the
277 bacteria.

278 8. Sialidase as therapeutic target

279 In human genome, four sialidases homologs such as NEU 1, NEU 2, NEU 3 and NEU 4 are
280 identified. All these enzymes have different substrate specificities [54,55]. Some of the examples of
281 sialidases as therapeutic targets are given below,
282

283 Sialidase activity on cancer cells shows that all the four types of sialidase homologs behave in
284 different manners in carcinogenesis [56]. Out of these four, NEU 1, NEU 2, NEU 4 shows a down
285 regulation with suppression of metastasis and tumor progression [57,58], while NEU 3 shows a

286 tendency of up – regulation [58]. Further pathological studies of NEU 3 will help to know its
287 application in control of cancer cells [54].
288

289 Epilepsy is seizure disorder that causes abnormal or excessive activity of brain cell. This
290 neurological disorder is characterized by unprovoked, recurrent seizures. It can be fatal if untreated
291 [59,60]. There are many reasons for epilepsy being difficult to be treated. One of the ways to treat the
292 anomalous neuronal disorder is by altering the activation of sodium channel through the negative
293 surface charged residues of cellular membrane from sialic acid. This method of modulating negative
294 surface charge of sialic acid can be a therapeutic target to treat epilepsy [61,62].
295

296 Influenza is viral infection affecting 5% of adults and 20% of children worldwide every year [63].
297 It is caused in the respiratory system affecting brain, kidney, heart, lung, liver and muscles [64].
298 DAS181 is a novel sialidases fusion protein which is used as a therapeutic target for Influenza [65].
299 DAS181 inactivates the receptors of the host cell that are identified by the viruses, by cleaving the
300 sialic acid from the host cell surfaces through making the host more repellent to the viruses [66,67].
301 Zanamivir and Oseltamivir are the competitive sialidase inhibitors thereby reducing its severity and
302 duration of the illness [68].
303

304 Pneumonia is caused by *Streptococcus pneumoniae* that is causes sepsis, meningitis after influenza
305 infection [69]. Similar to Influenza virus, *S. pneumoniae* possess sialidase activity [70]. Biofilm is
306 important for the pneumococcal colonization. Nan A and Nan B (the gene that encodes enzymes
307 in sialic acid pathways) expressions is up – regulated in biofilm formation in pneumonia and also the
308 mutants shows a reduced ability to form biofilm thereby reducing the development and severity of
309 pneumonia [31,71,72].
310

311 Periodontitis is a chronic oral inflammatory disease that initially causes infection in the tooth
312 pockets eventually leading to tooth loss [27]. Two major pathogens that causes periodontitis are
313 *Porphyromonas gingivalis* and *Tannerella forsythia* [73]. *P. gingivalis* and *T. Forsythia* possess
314 neuraminidase activity that inhibits the biofilm formation but yet the pathological role of the sialic
315 acid enzyme is yet to be discovered [74,75].
316

317 Apart from the above disease, sialidase is used as a therapeutic agent in *Bacterial vaginosis* [76–
318 78]. Cystic fibrosis [79–81], Chagas disease [82,83] and in other bacterial and viral disease. Therefore,
319 sialidases are at an infancy level to be used as therapeutic target.

320 9. Conclusion

321 Bacterial sialidases and their sialoglycan targets contribute to host–microbe interactions at the
322 mucosal surface. Such mechanisms play a pivotal role in both the oral and gut microbiome where
323 there is rich mucin environment and profuse sialoglycoproteins in the saliva and in the gut mucus
324 respectively. An imbalance in the proportion of gut commensals able to modulate mucosal sialic acid
325 levels or a change in host mucin sialylation is often associated with enteric infection or intestinal
326 inflammation. Maintaining a balance in the ability of commensals to produce and/or consume sialic
327 acid in the mucosal compartment is therefore essential to oral and or gut homoeostasis.

328 Further investigations of bacterial sialidases should clarify the type of sialylated structures that
329 are accessible to the bacteria and the specificity of sialidases towards sialic acids with different
330 modifications and in different linkages. These include gaining structural insights into the diversity of
331 sialic acid derivatives that can be produced and/or taken up by commensal and pathogenic bacteria.
332 Thus, for therapeutic purposes, modulation of sialidase expression might be effectively achieved by
333 appropriate use of specific inhibitors or pro/prebiotic approaches targeting specific bacterial strains.
334 This approach will play a role in reverting dysbiotic infections.
335

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