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Reviewer 2

The review on "Streptococcus gordonii: Pathogenesis and Host Response to its Cell Wall Components" seems to comprehensively summarize the known cell wall components and their role in host interaction.

The manuscript would benefit from a thorough review of English expression and addressing the following minor changes:

Page 1 line 42/43: Streptococcus gordonii is not a typical resident of the gastro-intestinal tract but typically found in the oral cavity. Pls revise the sentence to reflect this better or combine with subsequent sentence, which correctly states that S. gordonii primarily inhabits the oral cavity.

We appreciate the Reviewer's critical comment. We agree to the comment and decided to delete the "and gastrointestinal tract".

Page 2 line 62: "streptococcal surface A" should read "streptococcal surface protein A".

We corrected it to "Streptococcal surface protein A".

Page 3 – Legend Figure 1: The legend (and also the text) should clarify more detailed that Streptococcus gordonii is a commensal of the oral cavity that can act as an opportunistic pathogen to cause oral disease and when disseminated through the bloodstream can cause serious infections at extra-oral sites.

We appreciate the Reviewer's constructive comment. In order to clarify it, we modified the following sentence in the revised manuscript.

(Line 77 at Page 3) "*S. gordonii*, a commensal bacterium, is found in areas of the human body such as the oral cavity and skin. It is also opportunistic pathogen associated with several diseases. In the oral cavity, *S. gordonii* is known to be closely associated with apical periodontitis. In addition, it can go through the blood stream by oral trauma and tooth extraction and disperse into various organs potentially causing systemic diseases including endocarditis, empyema, perihepatic abscesses, and pyogenic spondylitis or spondylodiscitis."

Page 3 – Lines 78-81: The initial sentences of the section on Apical Periodontitis are confusing as they mix up two diseases (apical periodontitis and periodontitis) that affect the periodontal tissues but typical differ in origin. In contrast to apical periodontitis, which as the authors correctly state originates from infected pulp tissue, periodontitis result from migration of tooth-associated biofilm bacteria into the gingival sulcus. The latter results in tissue detachment from the tooth and formation of gingival pockets and eventual tissue invasion by bacteria. The sentence "According to study from the Centers for Disease Control

and Prevention in the US, 47.2% of adults have periodontal disease with prevalence rates increasing to 64% in adults 65 years of age and older." should be removed as it does not refer to apical periodontitis.

We appreciate the Reviewer's constructive comment. We modified the sentences in the revised manuscript as suggested.

(Line 95 at Page 4) "A study in the US has revealed that 4.1% of randomly sampled teeth have apical periodontal disease, and this rate increases upto 31.3% from teeth receiving endodontic treatment [19]."
(Line 107 at Page 4) "Furthermore, the biofilm formation of *S. gordonii* on dentin surfaces facilitates invasion into the dental pulp through dentinal tubules [24]. In addition, *S. gordonii* can interact with host cells followed by its penetration into root canals or dentinal tubules [18]."

The second paragraph of the same section contains a lot of mixed statements that refer to periodontitis instead of apical periodontitis. This should be streamlined to distinguish that while S. gordonii enables attachment and colonization of the gingival crevice by the periodontal pathogen Porphyromonas gingivalis, it is not considered a periodontal pathogen itself.

We apologize for the inappropriate contents and references. As suggested, we modified the sentences that only refer to apical periodontitis and replaced with appropriate references in the revised manuscript.

(Line 118 at Page 5) "Moreover, *S. gordonii* also induces the expression of IL-8 in human endothelial cells [27]"
(Line 121 at Page 5) "The presence of pro-inflammatory cytokines has been reported in apical periodontitis lesions [30,31]"

Page 3 – line 88: It is not clear what the author s mean by "…..34% out of various microbial compositions …."
We appreciate the Reviewer's critical comment. Chavez de Paz *et al*. investigated the diversity among streptococcal species isolated from root canals with apical periodontitis receiving endodontic treatment (Oral Surgery Oral Medicine Oral Pathology Oral Radiology 2005, 100:232-241). They analyzed the root canal samples from a total of 100 patients. In 34 out of 100, *S. gordonii* was isolated. In order to clarify it, we modified the following sentence in the revised manuscript.

(Line 96 at Page 4) "*S. gordonii* was predominantly isolated from 34 of 100 patients with apical periodontitis [10]."

Page 4 – line 108: "….. etiological bacterium ….." reads awkward – could be changed to " ….. etiological agent …"

As suggested by the Reviewer, we changed it to "etiological agent" in the revised manuscript.

(Line 128 at Page 5) "Therefore, *S. gordonii* is considered as an etiological agent that

contributes to the development of apical periodontitis and alveolar bone resorption through the induction of acute inflammatory conditions."

Page 4 – line 113: "Infective endocarditis is a representative life-threatening disease caused by oral streptococci ……" – remove "representative" from the sentence.

As suggested, we omitted the "representative".

Page 4 – line 115: remove "study" from the sentence as it is redundant with "analysis".

As suggested, we omitted the "study".

Page 7 – line 221: "… S. gordonii similar to Enterococcus faecalis …." needs an article to read " …. S. gordonii similar to the Enterococcus faecalis ….".

We added an appropriate reference (Journal of Endodontics 2013, 39:39-43) in the revised manuscript as follows:

(Line 251 at Page 10) "CbdA is a protein of *S. gordonii* similar to *Enterococcus faecalis* collagen-binding protein, Ace in the structure and function [77]."

Page 8 – line 257: The word "exceptionally" should be remove from "However, exceptionally, S. aureus has been reported …"

We appreciate the Reviewer's comment. This comment is similar to the third reviewer's comment that the sentence should be deleted. Therefore, we omitted this in the revised manuscript.

Page 12 - 4.1. Disruption of adherence: this paragraph can be removed as it only lists adhesins that have been explained before and the only relevant statement is the last sentence, which acknowledges that there is currently no known agent for disruption of adherence. Such as statement can be integrated in other parts of the review - e.g. 4.2 Regulation of Biofilm

We appreciate the Reviewer's critical comment. Considering Reviewer's comment, this paragraph was inserted into the part of "Regulation of biofilm".

Page 13 – the word control in the headers for sections 4.3.1 through 4.3.3 should be replaced by a more appropriate term such as for example "Lipoproteins as therapeutic targets" instead of "Control of lipoproteins"

We appreciate the Reviewer's comment. This comment is similar to the third reviewer's

comment that the “control of” should be deleted. Thus, we deleted it.

- Thank you -