Porphyromonas gingivalis gingipains modulate host translational control during oxidative stress

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1.0 Introduction

Periodontitis is an inflammatory disease affecting ~743 million people worldwide[1] and is characterised by receding and bleeding gums (Fig. 1). It is associated with the invasive bacterium *Porphyromonas gingivalis*[2]. Upon infection, *P. gingivalis* secretes proteases known as gingipains that degrade a variety of host cell proteins including the mammalian target of rapamycin (mTOR), a protein essential in several cellular processes including cell proliferation, cell survival and autophagy[3]. Studies have shown that the bacterial pathogen *Shigella flexneri* infection activates and dysregulates the integrated stress response (ISR) via a pathway involving mTOR and leads to the modulation of stress granule formation[4,5,6]. Given that *P. gingivalis* targets mTOR, we hypothesised that *P. gingivalis* may dysregulate the ISR and this may contribute to its pathomechanism.

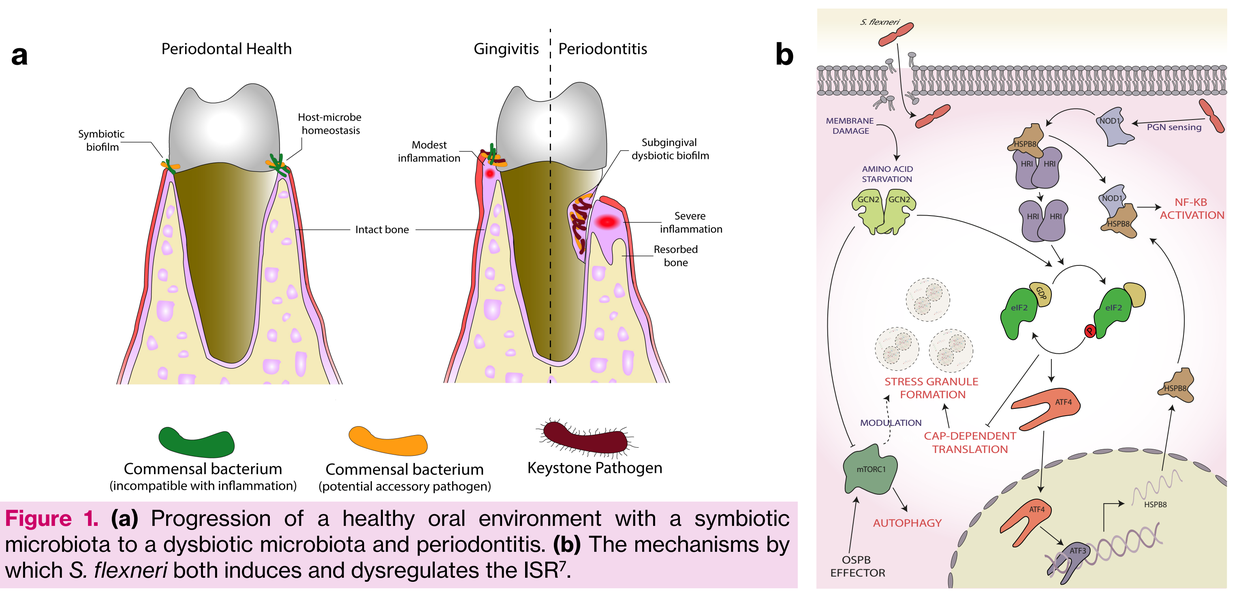

Figure 1. **(a)** Progression of a healthy oral environment with a symbiotic microbiota to a dysbiotic microbiota and periodontitis. **(b)** The mechanisms by which *S. flexneri* both induces and dysregulates the ISR[7].

2.0 Aims & Objectives

1. The impact of *P. gingivalis* infection on protein synthesis
2. The mechanism of protein synthesis modulation
3. The impact upon stress granule formation

3.0 Findings and Conclusions

P. gingivalis infection does not induce ISR activation. However, in response to exogenous stress, proteases secreted by *P. gingivalis,* termed gingipains, heighten stress induced translational stalling. As the lysine specific gingipain is known to degrade mTOR[3], the lysine gingipain modulation of stress granule formation, is likely mediated through the mTOR axis.

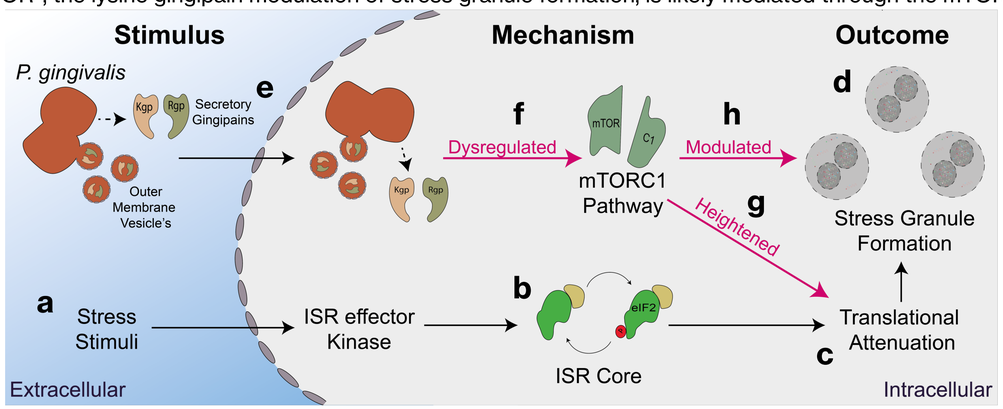

Figure 2. **(a)** Stress inhibits activates an ISR effector, which **(b)** phosphorylates eIF2 **(c)** leading to translational attenuation and **(d)** stress granule formation. **(e)** *P. gingivalis* excretes gingipains (freely and encased in outer membrane vesicles) in an extra and intracellular manner, which **(f)** dysregulate the mTORC1 pathway leading to **(g)** heightened translational repression and **(h)** modulated stress granule formation.

4.0 Don Whitley A25 Anaerobic Cabinet

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This study investigated interactions between *P. gingivalis* and host translational control during oxidative stress.

P. gingivalis is a facultative anaerobic bacterium and as such requires culture under strictly anaerobic conditions.

To produce reliable anaerobic culture conditions a Whitley A25 workstation was employed. The oxygen monitoring system and log provided peace of mind, confirming that cultures had been optimally cultured, ultimately producing uniform culture viability and reproducible results.

4.0 References

[1]Tonetti *et al.,* (2017). *J. Clin. Periodont.* **44**(5), 456-62. [2]Hajishengallis. (2015). *Nat. Rev. Immunol.* **15**(1), 30-44. [3]Stafford *et al.,* (2013).*Mol. Oral Microbial.* **28**(5), 366-78. [4]Vonaesch *et al.*, (2016). *Cell. Micro.,* **18**(7), 982-99.[5]Tattoli *et al.*, (2012). *Cell Host & Microbe*, **11**(6), 563-75. [6]Abdel-Nour *et al.,* (2019). *Science.* **365**(6448), eaaw4144. [7]Knowles *et al.,* (2021). *Front. Microbiol.,* **12**, e645161.