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Commentary

The Chicken or the Egg? Changes in Oral Microbiota as Cause or Consequence of Mucositis During Radiation Therapy

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Oral mucositis remains one of the most dominant, serious, disruptive, and symptomatic complications of radiation therapy used for the treatment of cancers of the head and neck (Villa and Sonis, 2015). Progressive mucosal injury accompanies increasing daily radiation fractions until confluent, deep, ulceration develops in the majority of patients, and the lack of an effective intervention is one of the biggest clinical frustrations for healthcare professionals charged with caring for them. Given the breadth of microbial colonization in the oral cavity, a role for the oral microbiome in altering the risk or course of mucositis has been suspected for years. And while the literature is replete with reports demonstrating a change in the composition of the oral flora following cancer therapy (Hu et al., 2013), anti-bacterial treatment strategies for mucositis have been largely unsuccessful (Trotti et al., 2004). A consistent and clinically meaningful link between the oral microbiome and mucositis has been elusive.

The historical paradigm for radiation-induced tissue injury, which was predicated on indiscriminate clonogenic cell death of rapidly dividing normal cells, has been overturned in favor of a more complex biological cascade (Sonis, 2009). How, if, and where the oral microbiome contributes to this scheme was the subject of a study reported in this issue of *EBioMedicine* by Zhu et al. (2017) who prospectively evaluated the relationship between the trajectory of changes in the oral microbiome and oral mucositis in nineteen patients being treated with radiation or concomitant chemoradiation for nasopharyngeal carcinoma (NPC). Thirteen of the studied subjects developed severe mucositis. Differences in the baseline (pre-radiation) oral microbiota were noted between control and NPC subjects: not only was there more similarity in the bacterial communities among healthy patients, but the healthy controls also had a more diverse microflora. Speciation of the oral flora among patients with no or mild mucositis differed from those developing more severe forms of the condition. This observation leads to key questions of its clinical significance: does it represent a means for facilitation of mucositis and is it specific enough to predict the course of mucositis, or do changing bacteria simply reflect the microflora's response to other, non-mucositis, but parallel factors?

The mucositis puzzle is complicated and consists of multiple pieces which not only fit together, but actively interact. Since the oral microbiome represents only one element of the puzzle, other pieces require consideration as, in the context of the Zhu et al. paper, they might provide additional or alternative explanations for the observations noted. The oral microbiome is varied and preferentially colonizes different sites in the mouth (Aas et al., 2005). Consequently, sampling biases or variation might impact how speciation reports differ. This presumes that, if certain species of oral bacteria are more likely to impact mucositis risk and course than others, longitudinal study of high risk sites would be most informative. On the other hand, if, as Zhu et al. conclude, oral bacteria secondarily colonize already ulcerated mucosa, those species capable of sustaining or stimulating a pro-inflammatory response, such as gram negative organisms, could be potential modifiers of mucositis course. While there seems to be little doubt that the flora of patients not being treated for cancer and those who are being treated is different, the question arises as to why.

Changes in the oral flora of cancer patients occur in a multifarious local and systemic environment. Even with radiation doses as low as 10 Gy, the volume and composition of saliva is altered. The degree of xerostomia, like mucositis, is radiation dose-dependent (Buglione et al., 2016). It is possible that the changes in the oral flora noted by Zhu et al. were a consequence of changes in salivary function resulting in less buffering, flushing, and immune function, and a surrogate from cumulative radiation dose. It is also possible that xerostomic changes modified mucosal health making it more susceptible to injury.

While this paper focused on the microflora, it is impossible to ignore the intrinsic contribution of the host as an element in mucositis risk. Radiogenomic data strongly suggest a genomic underpinning to individual patient response to radiation with respect to tissue injury (Pratesi et al., 2011). While these findings are clearly relevant in the case of mucositis, they also raise the likelihood that genomics impact patients' reactions to specific bacterial species resulting in a lack of uniformity in how individuals respond to colonizing bacteria. For example, while Zhu et al. noted that increases in *Streptococcus mitus* were associated with the development of severe mucositis, De Ryck et al. contrastingly reported that, in a mucosa co-culture model, *Streptococcus mitus* markedly enhanced epithelial wound healing (De Ryck et al., 2015).

Host contributions to flora changes are reflected by the substantial body of data demonstrating that neutropenia impacts the oral microbiota

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and, in particular, predisposes to increases in gram negative organisms. Leukopenia is a recognized side effect of head and neck chemoradiation regimens (Xu et al., 2017). And while not noted by Zhu et al., the finding that concomitant chemoradiation regimens are typically more mucotoxic than those of radiation alone suggests that neutropenia impacts the course of mucositis. The inclusion of such data in future studies would be informative.

The fundamental question raised in this paper is associated with the potential etiologic role for the oral microflora in the development and/or progression of mucositis. While there seems to be no doubt that changes in the oral microbiome occur during cancer treatment, the lack of an assessment and analysis in which each potential influential element is comprehensively assessed in the context of a patients' clinical course precludes actionable conclusions. The provocative study by Zhu et al. is illustrative of the potential for further investigations. While it seems clear that changes in the oral microbiota associated with head and neck radiation therapy are potentially biologically relevant to mucositis, it is unclear how these changes influence its course.

Disclosure

No conflicts of interest to declare.

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