J. Bowen, N. Al-Dasooqi, P. Bossi, H. Wardill, Y. Van Sebille, A. Al-Azri, E. Bateman, M. E. Correa, J. Raber-Durlacher, A. Kandwal, B. Mayo, R. G. Nair, A. Stringer, K. ten Bohmer, D. Thorpe, R. V. Lalla, S. Sonis, K. Cheng, S. Elad . On behalf of The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO)

The pathogenesis of mucositis: updated perspectives and emerging targets

Supportive Care in Cancer, 2019; 27(10):4023-4033

The pathogenesis of mucositis: Updated perspectives and emerging targets

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Affiliations

Hannah – 1) Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia, 2) Department of Paediatric Oncology/Haematology, The University Medical Centre Groningen, Groningen, The Netherlands

Corresponding Author:

Associate Professor Joanne Bowen

Adelaide Medical School

University of Adelaide

Tel: +618 8313 1374

Email: joanne.bowen@adelaide.edu.au

Introduction

The MASCC/ISOO Mucositis Study Group periodically reviews the literature relating to mucositis pathogenesis, mechanisms and novel therapeutic approaches, and distils this to summary perspectives and recommendations for research. Continuing this tradition, in 2017, 164 articles published between January 2011 and June 2016 were identified by systematic review and critiqued by 15 reviewers in a bid to uncover progress made, and highlight new targets for further investigation. Moreover, all findings have been assessed in the context of the current state of knowledge discussed in the previous reviews (Al-Dasooqi et al., 2013, Anthony et al., 2006, Sonis et al., 2004). The approach differed slightly from the last guidelines that reviewed 90 articles, in that each paper was critiqued by one reviewer compared to two previously due to the substantial increase in new literature that needed to be included, although all other aspects including the key search terms, databases included, and the review form were unchanged (for further details see (Al-Dasooqi et al., 2013).

In the previous review, a summary of the key mediators of mucosal toxicity was provided including a discussion of the role of tissue structure (including the extracellular matrix and epithelial tight-junctions [TJ]), inflammation, and the microbiome. In addition, discussion also focused on emerging understanding of the toxicities associated with targeted anti-cancer agents, toxicity clusters, biomarkers of mucosal injury and risk prediction of mucosal injury. Collectively, this was an exhaustive summary of the state of the field when published. This update aimed to provide a perspective on advances and momentum shift since 2011 in regards to understanding the pathogenesis (Table 1).

Emerging and established mediators of toxicity

Microbiome and host immune response

Whilst in 2013 the literature described shifts in oral and GI flora being associated with mucosal injury, what can now be appreciated is that there is a complex interaction between the baseline composition of diverse species, as well as encompassing dynamic changes as a result of cancer treatment. Patient studies have looked at overall diversity of oral flora and shifts during chemotherapy (Ye et al., 2013) to determine relationships with oral mucositis. In vitro models of oral keratinocytes have also been used to demonstrate how microbes impact healing (De Ryck et al., 2014, De Ryck et al., 2015), as well as the functional changes to the microbes themselves during exposure to irradiation (Vanhoecke et al., 2016, Vanlancker et al., 2016). The field has also been advancing rapidly in the area of intestinal mucositis, where microbial dysbiosis measured in easily accessible fecal samples has led researchers to postulate that gut microbiome composition can be used as a surrogate marker for changes leading to diarrhea (Wang et al., 2015). Furthermore, there appears to be mechanistic linkages with altered microbial signatures during high dose chemotherapy and ability to metabolise nutrients and xenobiotics (Montassier et al., 2015).

Whilst it would be presumptuous to directly compare microbial composition in humans to animal models of mucositis, there has been some evidence of overlapping features that are commonly seen and could be used for comparative studies. This includes the observation of a general decrease in microbial diversity seen following cancer treatment (Pontoppidan et al., 2015, Lin et al., 2012, Nam et al., 2013), and a shift towards increased relative proportions of proteobacteria which include facultative anaerobes such as E. coli and salmonella (Stringer et al., 2013, Lin et al., 2012, Nam et al., 2013, Montassier et al., 2014). Given these overlaps, it encourages exploring the relationship between microbiome shifts and mucositis further in animal models.

Opportunities for targeting microbial-mucosal interactions has been elegantly demonstrated with the emergence of genetic knock out models of mucositis. The toll-like receptors (TLRs) have been a major area of focus due to their direct interface between microbial ligands and signaling cascades through epithelial, neural and immune cells (Cario, 2016). In the context of irinotecan-induced

intestinal mucositis, germ-line deletion of TLR4 is protective (Wardill et al., 2016), as is MYD88 (Wong et al., 2015) which is the main adapter protein for all TLRs. However, protective effects of TLR deletion can be receptor and drug class-specific. For example, methotrexate-induced intestinal mucositis is exacerbated in TLR2 knock out mice, a phenotype that is corrected when the co-receptor MD2 is also deleted (Frank et al., 2015), yet TLR2 knock out is protective against irinotecan-induced mucositis (Wong et al., 2015). In contrast, TLR2 deletion and TLR9 antagonism is protective against doxorubicin-induced intestinal mucositis (Kaczmarek et al., 2012). Evidence for a direct contribution of the intestinal microbes was demonstrated in germ-free mice which were protected against irinotecan-induced mucositis, but lost protection when colonised with a diverse microbiome (Pedroso et al., 2015). Furthermore, the contribution of B-glucuronidase producing microbes was shown to be associated with the development of mucositis, but not wholly responsible (Pedroso et al., 2015).

TLR agonism may also be protective in some settings. The TLR5 agonist, CBLB502, was shown to reduce radiation-induced oral mucositis (Burdelya et al., 2012), whilst the natural ligand, flagellin, protects against radiation-induced intestinal injury (Jones et al., 2011). A TLR9 agonist could protect against lethal doses of whole body and abdominal radiation in mice (Saha et al., 2012). Finally, addition of lipopolysaccharide (LPS), the cogent TLR4 agonist, prior to abdominal radiation has previously been shown to reduce radiotherapy-induced mucosal barrier injury via a cyclooxygenase-dependent manner (Riehl et al., 2000). Whether TLR agonism confers direct protection to the epithelium or via resident microbes is still to be shown. However, this does support recent evidence that consumption of probiotics can dampen mucosal injury following diverse cancer treatments (Bastos et al., 2016, Ciorba et al., 2012, Justino et al., 2014, Tang et al., 2016, Xie et al., 2016, Yeung et al., 2015, Yuan et al., 2015, Wang et al., 2013a). The evidence for probiotics is strongest in the setting of pelvic radiation (Gibson et al., 2013, Lalla et al., 2014a), and this suggests that the protective effects in rodent models of radiation-induced mucositis may be translated to the clinic. The potential mechanisms may relate to TLR agonism by gram-positive species such as Lactobacillus.

However, given the variability in outcomes of probiotic clinical trials, much more exploratory work is needed to fully understand the microbial-mucosal interactions specific to mucositis pathogenesis.

In contrast to intestinal microbiota, there were a lack of research articles exploring relationships between oral microbial composition and development of oral mucositis published during the review period. Although generally agreed that the oral microbiome plays a role in the susceptibility to, and infectious consequences of ulcerative mucositis, as well as being altered by cancer treatments, there is a lack of mechanistic understanding (Vanhoecke et al., 2015). Two studies explored changes in oral microbial composition during treatment and identified potential species important for mucositis pathogenesis (Ye et al., 2013, Laheij et al., 2012), although these included different cohorts and detection methods. As such, further work is required to unravel the complexities regarding the oral microflora and mucositis.

~~Globally, microbiota composition and richness have been shown to influence the sensitivity to inflammation of the intestinal mucosa. The oral microflora has a different composition and a high complexity, and it is similarly influenced by the treatment. However, different bacterial species exert their activity in determining the risk and severity of mucositis, and their role needs to be further studied.~~

The emerging potential to manipulate the microbiome with new treatments beyond the current concept of probiotics and prebiotics also delineates a clear path forward. As such, we should now consider the role of the microbiome in all phases of mucositis pathogenesis (Figure 1), rather than viewing it as a passive contributor of the ulcerative phase.

Sophisticated targeting of inflammation

The previous review identified inflammation as central to mucositis pathogenesis and expanded on the role of pro-inflammatory cytokines and NF-kb signaling (Al-Dasooqi et al., 2013). Although based

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on a sound scientific rationale, the approach to inhibition of these pathways, such as with pentoxifylline and celecoxib, has thus far poorly translated from the preclinical (Frings et al., 2016, Gruber et al., 2015a, Gruber et al., 2015b) to clinical setting (Lalla et al., 2014b, Jensen et al., 2013). Newer studies have continued to investigate the potential for use of anti-inflammatory agents for mucositis management in preclinical models, although focused on broader outcome measures to link effectiveness with mechanisms. Since the last pathogenesis update there have been two preclinical studies testing IL-1ra, the naturally occurring IL-1 antagonist (Wu et al., 2011a, Wu et al., 2011b, Xiang et al., 2011). Both studies found protection against chemotherapy-induced intestinal mucositis and crypt destruction in the small intestine which was attributed to apoptosis prevention.

Other protein-based anti-inflammatory therapy have included antibodies against chemokines, CXCL4 (Gao et al., 2014) and CXCL9 (Lu et al., 2015), indicating a more sophisticated knowledge of the immune contributors to mucositis pathogenesis and how it could be more precisely targeted. Downstream of TLR activation is the well-characterised upregulation of NFkB-dependent cytokine production; targeting these downstream mediators, for instance by knocking out IL-4 (Soares et al., 2013), is protective in rodent models. This might emerge as the preferred technique when translating this to the clinic since it has been recently suggested that intact TLR signaling is necessary for adequate anti-tumour responses to chemotherapy and immunotherapy (Li et al., 2017).

Cell-based approaches to established inflammation management have recently emerged and present a paradigm shift from the traditional protein and pharmaceutical compound mode of mucositis therapy. M*esenchymal stem cell (MSC) therapy* has been investigated in autologous transplant to pigs and rats with radiation-induced proctitis (Linard et al., 2013, Linard et al., 2016); transplant of human umbilical cord MSCs to mice with radiation-induced intestinal mucositis (Wang et al., 2013b) and guinea pigs with radiation-induced oral mucositis (Duan et al., 2015); and finally, adipose-derived MSCs have shown effectiveness for resolving radiation induced colonic inflammation (Bessout et al., 2015). The utility of MSCs to prevent oral mucositis induced by

fractionated radiotherapy has also shown promising results in mice; interestingly, the positive modulation was dependent on the timing of MSC transplantation (Schmidt et al., 2014). Collectively, this provides some early evidence for MSC therapy in both the setting of acute and chronic radiation-induced inflammation and with either bone marrow derived or peripheral sources of stem cells. However, whilst promising results thus far in some preclinical models of established inflammation, translation to the clinic will require longer term safety and further efficacy studies.

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Altered functional physiology

Diarrhea occurs when there is unmatched absorptive and secretory capacity of the intestines, often due to enhanced motility or presence of osmotically active or inflammatory luminal contents. Clinical anti-diarrheal agents target secretory process and motility, yet there is a lack of attention in preclinical models on these as outcome measures (Grover et al., 2016, Sanchez-Lara et al., 2013). Models capable of assessing absorption of nutrients have been recently developed (Fijlstra et al., 2015, Fijlstra et al., 2013, Fijlstra et al., 2011), and the role of secretory processes has been extensively profiled in models of inflammatory bowel disease (Gareau and Barrett, 2013). However, there is a dearth of papers that have directly examined changes in motility in response to cancer therapy, both in preclinical models and the clinic. Some papers have recently assessed changes in enteric neuron populations following chemotherapy (McQuade et al., 2016, Robinson et al., 2016) and provide mechanistic insight to the underlying functional changes. Furthermore, neural-support cells, enteric glia, have been shown *in vitro* to mitigate altered permeability following exposure to inflammatory cytokines (Cheadle et al., 2013). Collectively, the role of motility and particularly enteric neurons in the pathogenesis of mucositis is an under-researched field that has the potential to uncover new therapeutic targets aimed at underlying functional dysfunction in the intestines during mucositis.

Chemotherapy and radiation has been known to alter TJs and increase intestinal permeability for decades (Melichar et al., 2005). However, there have been recent advances in our understanding of the role specific TJs play and how intestinal permeability leads to not only microbiome translocation and subsequent activation of immune responses to mediate mucositis pathogenesis, but also may also be essential for systemic anti-tumour responses (Alexander et al., 2017). At the time of the last update, it was unknown to what extent TJ alterations contribute directly to clinical symptoms of mucositis. There was a single study showing an association between protection against oral mucositis and retention of TJ properties following radiation (Chen et al., 2011). Wardill and colleagues showed a relationship between endotoxin levels and diarrhea, which was linked to changes in TJs and FITC-dextran translocation (Wardill et al., 2014, Wardill et al., 2016). Further studies exploring the specific relationship between altered permeability and mucositis have been conducted by Biju et al, who used a surrogate maker for endotoxemia during radiotherapy in mice (Biju et al., 2012); Russo et al, who evaluated blood and urine markers of mucosal barrier injury in patients (Russo et al., 2013); and Beutheu et al, who showed that amino acid supplemented feed was protective against chemotherapy induced mucosal barrier injury in rats by preventing FITC-dextran translocation (Beutheu et al., 2014). Given that TJ loss is the preceding lesion to increased intestinal permeability, future research should measure the ability of mucositis interventions to stabilise these proteins as a routine outcome measure.

Photobiomodulation

Since the MASCC/ISOO clinical practice recommendation (Lalla et al., 2014a) that low-level laser therapy, now termed photobiomodulation, is recommended for the prevention of oral mucositis in HSCT (high-dose chemotherapy with or without TBI), further assessment of the mechanisms by which it is protective has been investigated in both *in vitro* and rodent preclinical models (Silva et al., 2015). This has elucidated that effectiveness of photobiomodulation may be specific to the

wavelength (Isman et al., 2015, Usumez et al., 2014), total dose, distribution over time and surface-, and class of laser treatment (Ottaviani et al., 2013). These can differentially activate tissue growth factors critical in healing and provide variable induction of endothelial repair. However, difficulties in interpretation remain due to the lack of consistency between photobiomodulation regimens in terms of the energy dose, duration and laser source, and in the mucositis models employed which have variable modes of causing oral ulceration.

Potential insights from technological advances in mucositis research

Efforts to replicate the complexities of the mucosa has led to the emergence of novel i*n vitro* models of mucositis. Gut-on-a-chip and other microfluidic style technology (Kim et al., 2016) provides opportunities to ask more sophisticated questions in a physiologically relevant environment consisting of multiple cell types that differentiate into mature intestinal structures over long term culture. Human cell, 3-dimensional, tissue models of oral mucosa (Colley et al., 2013, Lambros et al., 2015a, Lambros et al., 2016, Lambros et al., 2015b), and the role of co-culturing with microbial biofilm (De Ryck et al., 2014) provide a more comprehensive interaction of factors related to radiation-induced mucositis pathogenesis. Finally, intestinal organoids; crypt structures formed by stem cells from either humans or mice, can be genetically manipulated for expression of factors important in mucositis pathogenesis (Chang et al., 2016, Grabinger et al., 2016, Liu et al., 2016). It is expected that these approaches will overcome the reliance on monoculture models and rodents which been used in the past and provide an incomplete view of dynamic interactions between tissues during mucositis development, or lack translatability between animal and human settings, respectively.

Perspective

- Of the papers reviewed, there was a dominance of work carried out in rats and mice (over 100 papers); with a modest reliance on clinically derived research (~30 papers); and a paucity of human *in vitro* evidence which likely reflects the difficulty in conducting mucositis research in the clinic outside of traditional interventional clinical trials. Whilst we have evolved over the years from the separation of oral mucositis and GI mucositis to alimentary mucositis in terms of underlying pathobiology, the two are still overwhelming investigated in "silos". In addition, aspects such as the role of extracellular matrix in alimentary mucositis in the panel's opinion have not been significantly advanced since the last update. Models continue to be developed for investigation of single modality cancer treatments which no longer reflects current clinical practice. It would be of assistance to the field if future research incorporated combination of classes of agents when investigating both mechanisms of injury and new interventions. Investigation of natural agents and plant derivatives (Cheah et al., 2014, Davarmanesh et al., 2013, de Freitas Cuba et al., 2016, Koohi-Hosseinabadi et al., 2015, Sezer et al., 2011, Shi et al., 2016, Shin et al., 2013, Tang et al., 2014, Tanideh et al., 2014, Younes-Sakr et al., 2012, Zuo et al., 2015) has shown promise through protection from oxidative stress pathways in oral and gastrointestinal mucositis models. Yet the isolated active components and specific mechanisms of protection require further elucidation. Finally, whilst not addressed in this review, the issue of personalised medicine and mucositis risk prediction is still vital and needs urgent attention. Concurrently, knowledge gained can also be applied to the recently appreciated area of predicting response to mucositis interventions.

Take home messages

- Research momentum is accelerating for mucositis pathogenesis, reflected by the increased publications reviewed in this update compared to the previous effort. With this has come

utilisation of new models and interventions that target more specific mechanisms of injury. Technological advances have the potential to revolutionise the field of mucositis research.

- More effort is needed to establish transdisciplinary research teams to promote discovery as well as translation to the clinic of mucositis interventions. An excellent example of this approach has been superoxide dismutase which has combined discovery science and clinical research to rapidly bring an effective intervention to patients.
- Clear selection of outcome measures in animal models that reflect changes in clinical settings are needed to confirm effectiveness of new interventions. In particular, the non-invasive and dynamic measurement of intestinal changes, with peripheral and fecal compounds such as citrulline, FITC-dextran and calprotectin, should be included as standard. This will improve the ability to identify the most capable agents for translation to clinical trials.
- It will be vital to keep up with the emergence of novel regimens in the clinic (including immunotherapy) and understanding of increased complexity of mucositis pathogenesis related to combinations of traditional drugs, radiation and targeted agents.

Table 1: Evolution of the pathobiological model of mucositis

	2004 Sonis Model	2013 MSG Update	2018 MSG Update
Mucosally-restricted mechanisms	Direct cytotoxicity (irreversible DNA-strand breaks in basal cell populations leading to apoptosis) during **initiation phase**; mucosal atrophy in oral cavity and crypt ablation/villous blunting in GIT; non-DNA injury initiated through ROS production	Tight junction defects and epithelial barrier dysfunction highlighted as important factor in exacerbating injury; appreciation for cellular kinetics of ECM e.g. cell cytostasis, ↓fibronectin/↑collagen deposits during **primary damage response;** AMP18 received attention for ability to rescue epithelia.	Key mechanisms outlined in 2004 remain fundamental to initiation of injury. Functional appreciation for endotoxin and bacterial translocation, with subsequent innate immune activation.

Inflammatory-based mechanisms	NF□B- and NRF2-dependent damage response resulting in pro-inflammatory cytokine production and MMP **signaling**. COX2, MAPK and tyrosine kinase production underpin tissue injury. **Signal amplification** results in worsened injury.	IL-6, IL-1β and TNFα considered key inflammatory mediators; inverse role for anti-inflammatory cytokines suggested but only minimally investigated.	More complex understanding of inflammatory signaling. Specific targeting of downstream mediators (e.g. IL-1RA, IL-4) continues to support key role of pro-inflammatory cytokines in mucositis.
Host immune responses	-	-	Emerging role of TLRs in mediating mucosal injury indicated by genetic knockout studies and pharmacological interventions; role(s) in mucositis progression are receptor- and drug class-specific. Concern for translation as TLR signaling is necessary for adequate anti-tumor response.
Microbially-mediated mechanisms and host-microbe interactions	Colonization during **ulcerative phase;** translocation predisposes to infectious complications.	Dysbiosis of host microbiome (oral and GI) following raft of anticancer therapies; conclusions remains **correlative**.	Host-microbe interactions at baseline critical for treatment efficacy and toxicity (key interest for risk stratification and prediction); dynamic changes in resident microbes continue to be characterized with increasingly sophisticated techniques. Conclusions largely remain **correlative**.
Neuroimmune signaling	-	-	Possible involvement of enteric glia and neuronal cell populations; more research needed. GI motility following anti-cancer therapy remains poorly studied.
Other	Non-epithelial factors considered important: endothelial dysfunction and apoptosis, platelet aggregation, submucosal connective tissue alterations including fibroblast apoptosis; ECM remodeling and MMP signaling critical in **healing phase.**	Importance of symptom clusters and mucosally-derived inflammation highlighted.	Mesenchymal stem cells assessed for therapeutic efficacy.

Figure 1

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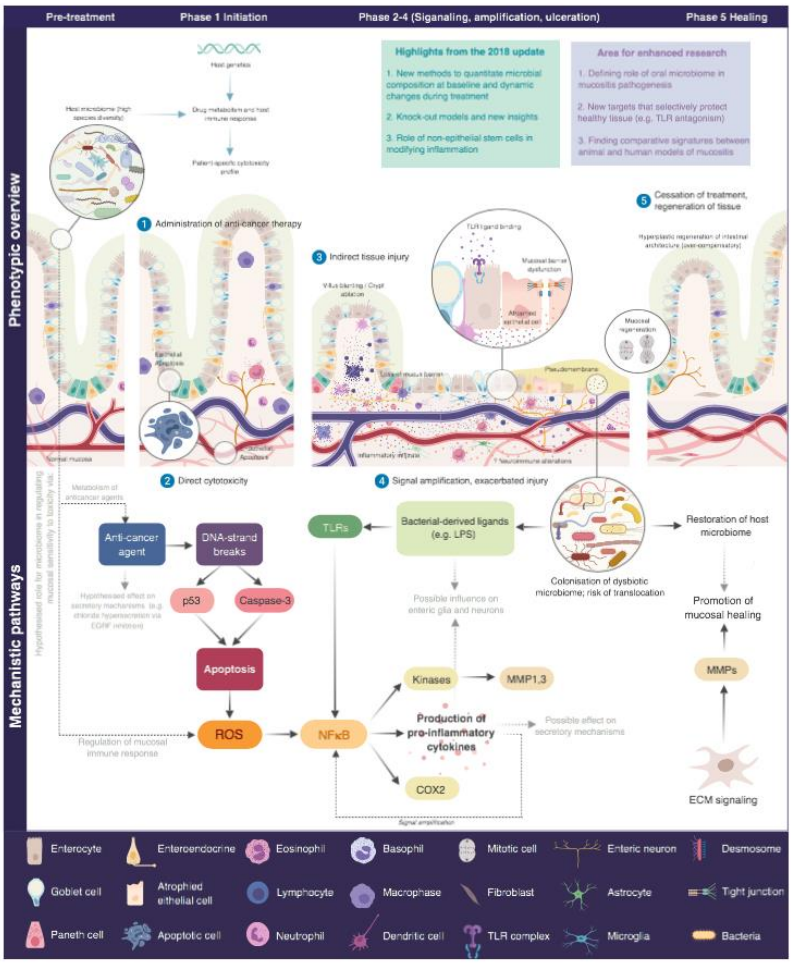

Fig 1. Impact of microbiota on all phases of mucositis, including pre-therapy risk. Some mechanisms likely overlap across regions of the alimentary canal, although the intestinal microbiome has been most extensively studied in recent literature.

Acknowledgements

Conflicts of Interest

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