The science of mucositis

Joanne Bowen¹ · Hannah Wardill^{1,2}

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The National Cancer Institute defines mucositis as a complication of some cancer therapies characterised by inflammation of the mucosal surfaces of the digestive system, often seen as sores in the mouth. This is similar to the definition introduced in 2006 by the National Centre for Biotechnology Information (NCBI), which includes atrophy of the squamous epithelium and vascular damage in addition to inflammation. The science underpinning these definitions has involved decades of clinical and preclinical research by investigators perplexed by the challenges faced to adequately predict, prevent, and manage this complication. This editorial aims to present a snapshot of some major milestone work that has moved our understanding forward and highlight where this has created promising new approaches to reducing the burden of mucositis.

Our initial understanding of mucositis was that it was caused by the non-specific actions of chemotherapy and radiation on susceptible epithelium, leading to cell death which was followed by inflammation due to breaches in epithelial integrity [1]. There has been evolving appreciation of the more complex and subtle nuances of the progression of injury leading to different presentations, as well as the development of “mucositis-like lesions” in response to the newer molecularly targeted and immune-based therapies [2]. As such, research now focuses on more than the absorptive epithelial lineage, but also immune and microbial contributions, the crypt niche supporting cells such as fibroblasts and secretory cells, and even neuroendocrine factors acting on enteric and autonomic nervous tissue [3].

The advent of technology that has enabled researchers to isolate specific pathways critical for mucositis development is arguably one of the most important developments in recent

times. Through a reductionist approach, this has included the use of genetically modified organisms, particularly rodent models, to uncover targetable signals and molecular drivers. Examples include toll-like receptor (TLR) pathway knockout models of mucositis, which have shown that although TLRs are key contributors, regulating the communication between the host’s immune system and microbial ligands to dictate inflammatory responses [4]. Importantly, they have receptor and context-specific actions, with deletion of TLR4, TLR2, TLR9, and the downstream adaptor protein MYD88 protecting against irinotecan-induced mucositis [5, 6]. Whereas TLR2 knockout exacerbates methotrexate-induced intestinal mucositis, although this is rescued when the adapter protein MD-2 is also deleted [7]. Augmenting these pathways in a translationally meaningful manner has proved challenging. As such, intelligent design of therapeutics to intervene in these pathways is required and may be suited to targets further down the pathway, including inflammatory mediators such as NF- κ B, which appear more ubiquitously associated with injury. Work using transgenic mice expressing nuclear protein Smad7 in keratinocytes has shown that antagonizing NF- κ B effectively prevents radiotherapy-induced oral mucositis [8]. Furthermore, Smad7 delivered as a local therapy also prevented oral mucositis in mice and dogs, and was able to significantly reduce epithelial apoptosis [9, 10], indicating improved translatability of this approach. Another well-characterised mediator of NF- κ B is oxidative stress mediated by reactive oxygen and nitrogen species, with oxygen radical scavengers and antioxidant enzymes showing promise against mucositis [11, 12]. One such agent, avasopasen manganese (GC4419), a superoxide dismutase mimetic, has shown promise in a large phase IIb clinical trial to reduce the incidence, duration, and severity of oral mucositis in patients with head and neck cancer treated with radiotherapy [13]. The confirmatory phase III trial (ROMAN; ClinicalTrials.gov identifier: NCT03689712) is currently underway with results expected in 2023, showing a clear example of how the science of mucositis can be translated to clinical therapeutics.

Another significant leap forward is the use of personalised medicine, revolutionised in main-stream cancer biology, in

✉ Joanne Bowen
joanne.bowen@adelaide.edu.au

¹ School of Biomedicine, University of Adelaide, Adelaide, Australia

² Precision Medicine (Cancer), South Australian Health and Medical Research Institute, Adelaide, Australia

supportive care research to identify those at risk of mucositis. This approach has been pursued with enthusiasm given the highly heterogeneous and unpredictable nature of mucositis, impacting our ability to intervene early and creating significant obstacles in clinical trial execution. There has been some evolution from linking single target polymorphisms with severe mucositis towards the unguided approach of transcriptomics and whole genome sequencing [14–16]. Mutations in drug metabolizing genes, including UGT1A1, DPYD, and MTHR [17–19], are associated with chemotherapy-related mucositis, but are infrequent and thus have limited clinical utility. Multiparameter risk prediction modeling is recommended, however uncommon reflecting the complexity of conducting such studies and prohibitive costs associated with analysis. Comprehensive genome-wide association studies have the potential to offer greater insight both pathobiologically and predictively [20]; however, they are relatively rare and yet to identify consistent targets. In contrast, a rapidly emerging target for risk prediction has been the gut microbiome, and the next logical step is to include microbiome sequencing and metabolomics to develop risk prediction algorithms. For this to be realised, appropriate infrastructure such as tissue and biome banking, and comprehensive data collection with skilled bioinformatics (likely with artificial intelligence and machine learning capacity) is needed to identify meaningful biomarkers with clinical utility. Although sequencing the microbiota genome (through technology such as 16S rRNA) is a relatively new approach to mucositis research, it has already yielded exciting findings that could be applied to personalised medicine and has the advantage of being a modifiable risk factor through microbial-related therapies such as ultra-narrow antibiotics, prebiotics, second-generation probiotics, and metabolites now being investigated in clinical trials [21–23]. Consequently, one of the major opportunities going forward is to begin to assess the impact of multiple mechanistic variables—genomics, proteomics, metabolomics, microbiomics—simultaneously in a systems biology approach to enact true personalised medicine in supportive care.

Concluding thoughts The Mucositis Study Group of MASCC has recently completed systematic reviews in the area of mucositis pathogenesis and mucositis risk prediction. Both have sought to shine a light on important and emerging approaches to better understand the key contributors to injury development and severity, as well as map out ways to identify factors associated with the highest risk of profound mucosal injury. It is expected that a number of the identified research priority areas in these papers will be seen in the form of early phase clinical trials as the science progresses through developmental pipelines. It will be crucial that pharmaceutical companies with mucotoxic anti-cancer drugs continue to invest in research that looks to minimise the occurrence and impact of mucositis in their patients, as

well as look for novel formulations that can avoid mucosal toxicity altogether. Treatments that are precisely targeted and timed to patients in need, that are effective, and without their own adverse effects are urgently needed.

The need to effectively intervene and control mucositis is further amplified as we begin to appreciate the breadth of secondary complications associated with breakdown of the oral and gastrointestinal mucosa. While it has long been appreciated that acute mucositis is by far the largest predictor of chronic gut dysfunction associated with pelvic radiotherapy, mounting data suggest that mucositis also predicts infection, graft versus host disease, malnutrition/cachexia, pain, fatigue, cognitive impairment, and even cardiotoxicity [24]. As such, a new frontier in the science of mucositis will be the interaction between acute and chronic toxicities, and the ability to mitigate chronic morbidity via the personalised prevention of acute injury. Notwithstanding these knock-on effects, managing the acute phase of severe mucositis requires intensive in-patient supportive care such as the provision of intravenous fluids and electrolytes, parenteral nutrition, and opioid analgesics and thus greatly impacts quality of life for weeks to months. Although clear economic data is hard to find, a cross-sectional in-patient database analysis from the USA found that over 11,300 adults were hospitalised with chemotherapy-induced ulcerative mucositis in 2017, with a mean length of stay of almost 9 days, at a cost of \$85,878 [25]. While this captures only a fraction of the number impacted by mucositis, it starts to present a picture of why this is a field that needs urgent attention, to not only decrease suffering by patients but also to mitigate huge economic costs to the sector. This is why the science of mucositis will continue to be a driving force to achieve success in protecting future patients from mucositis.

Declarations

Conflict of interest The authors declare no competing interests.

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