The Quest for Effective Treatments of Mucositis

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Commentary on "Animal Models of Mucositis: Implications for Therapy" by Joanne Bowen, Rachel Gibson, and Dorothy Keefe (page 161).

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Regimen-related mucosal toxicity (mucositis) is a largely unsolved medical need associated with cancer treatment. Despite its long history, patients continue to suffer and clinicians are frustrated by the diffuse, painful ulcerative lesions of the mouth, esophagus, intestine, and rectal mucosa that are commonly induced by a range of chemotherapeutics and radiation therapies and which largely defy effective intervention. This review by Bowen and colleagues largely captures the past and current roles animal modeling plays in regard to our understanding of mucositis and the quest for effective treatments.

Until the late 1990s the biological complexity of mucositis was underappreciated. Prior to that time, the condition was considered to be solely the consequence of nonspecific direct damage to rapidly dividing epithelial "stem" cells. Any thoughts of intervention were focused on palliation or modifying proliferating normal cells. Attempts to better understand the pathogenesis were largely limited to the use of cadaveric material.[1] The introduction of animal models enabled studies in which mucositis could be investigated at the tissue, cellular, and genetic levels and revealed biological targets for possible treatment.

Chemotherapy-induced mucositis has been effectively studied in the mouse, hamster, and rat. Early studies by Farrell et al,[2] which combined 5-fluorouracil (5-FU) and methotrexate to induce lesions of the small intestine, were important in establishing the kinetics of intestinal injury. Although largely superseded by new hamster models, the original 5-FU-induced mucositis model in that species was critical to providing insight into the pathogenesis of mucositis.[3] However, it was the advent and application of the acute radiation model in hamsters that provided the seminal data to support new mechanistic paradigms of mucositis biology at the cellular and genomic levels.[4,5] Importantly, the results of mechanistic and genomic studies in humans corroborated the original findings in hamsters.[6–8] The rat model introduced by Bowen and colleagues[9] has been instrumental in further defining the complex pathoetiology of chemotherapy-induced gastrointestinal mucositis.

With the completion of phase 2 and 3 clinical trials, assessment of the translational effectiveness of animal models is now attainable. Modeling of oral and intestinal chemotherapy- or radiation-induced mucositis by Farrell et al,[2] Dorr et al,[10] and Keefe et al[11] provided proof of concept for the clinical enablement of keratinocyte growth factor and confirmed information of value in establishing clinical dosing schedules. The hamster models of acute, fractionated, and chemoradiation-induced mucositis have proven to be predictive for the clinical response of at least two drugs and one biological: *N*-acetyl cysteine,[12] SCV-07,[13] and FGF-20.[14] In general, animal models have been most valuable in assessing potential efficacy and defining and optimizing treatment schedules.

As recognized in Keefe's dark agouti mammary adenocarcinoma model, one cannot ignore tumor response when studying potential mucositis interventions.[11] Before any agent can go from animal to human, it is critical that it not only shows a mucosal protection benefit but also that it fails to undermine the antitumor effects of either radiation or chemotherapy.

The candor with which Bowen and colleagues note the shortcomings of animal models of mucositis should be appreciated. Without question, both the science of mucositis and steps toward effective treatments have been furthered by the application of animal modeling. Nonetheless,

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the best model is the human. Hopefully, the fruits of animal studies will continue to yield effective therapy options for patients at risk of regimen-related toxicities.

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