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Editorial

Maestros of malignancy: Microbes as the conductors of carcinogenesis

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The first reported observation of a microbe associated with cancer was in 1890 when Dr. William Russell, a pathologist at the Royal Infirmary of Edinburgh, characterized unknown structures in a variety of cancers that he termed "fuchsine bodies" which retained fuchsine stain when slides were double stained with fuchsine and iodine green [1] He ultimately characterized these structures as having filamentous growth, spores, and growth within leukocytes in the cancerous tissue that he concluded was a fungus belonging to *Sprosspilze*. More than 130 years later our recognition and understanding of the finely orchestrated relationship of host microbes with carcinogenesis has grown tremendously. Once limited to colon cancer [2,3], the role for the microbiome to modulate a variety of non-intestinal cancers including breast [4], melanoma [5,6], and pancreas [7], as well as treatment response [8,9], has been better defined. In this special issue of *Neoplasia* entitled "Implications of the Microbiome in the Development, Progression, Treatment, and Prevention of Cancer", investigators provide ground-breaking work that expands the current knowledge of the microbiome in a variety of cancers, treatment response and toxicity, as well as nutrition. Furthermore, comprehensive reviews update readers on the state of the microbiome in microbiota-driven colorectal carcinogenesis, microbiome-derived biomarkers for early colorectal cancer detection, microbiome-innate immune interaction, among others. This special issue of *Neoplasia* aims to not only update the reader on recent research in this growing field of oncology but to provide a framework for education and exploration.

Perhaps one of the most notable areas of interaction of the microbiome in carcinogenesis is its relationship with the host immune system. Numerous studies have demonstrated the immunosuppressive effect that the microbiome can have on the tumor microenvironment, allowing avoidance of immune surveillance or reduction of immune cell killing [10]. Griffin and Hang provide an excellent review on the state of the microbiome in immunotherapy including a collated list of studies that sought to investigate this relationship [11]. Their review is germane to this issue in that Dr. Silver's group demonstrated that *Fusobacterium* is enriched in oral tongue cancer and that this enrichment resulted in increased PD-L1 mRNA expression [12]. Furthermore, this observation was corroborated *in vitro* with increased PD-L1 expression in human head and neck cancer cell lines. This suggests a potential modulatory effect of the oral microbiota on immunotherapy response in head and neck cancers. As further evidence for the relationship of the microbiota with the immune checkpoint pathway, PD-1/PD-L1, Peiffer et al. investigated the fecal and saliva microbiome of patients with metastatic castrate-resistant prostate cancer who progressed on standard enzalutamide therapy prior to treatment with the anti-PD-1 treatment, pembrolizumab [13]. Finally, Dr. Angel Charles presents a comprehensive review of the role of the microbiome to modulate the anti-tumor function of the innate immune system [14]. This is in contrast to most adaptive immunity-related studies and provides a framework for future investigations.

Investigations of the role of the microbiome in colorectal carcinogenesis continue to bring new knowledge but also highlight work still to be done. Dr. James Kinross and his team provide an outstanding systematic review of microbiome-derived biomarkers for early colorectal cancer detection providing evidence that while there is considerable heterogeneity in the queried studies, the fecal and oral microbiome may complement existing colorectal cancer screening techniques but is too immature for clinical use [15]. Dr. Shogan's group continue their progress characterizing the collagenolytic bacteria, *Enterococcus faecalis*, in that it is able to induce migration and invasion of colon cancer cell lines but that colon cancer cell invasion appears dependent on the collagenolytic properties of *E. faecalis* [16]. Furthermore, its ability to enhance migration appears dependent on the ability to activate pro-uPA. Finally, Bellerba et al. share the results of their phase II clinical study evaluating the interplay between vitamin D supplementation and gut

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microbiota alteration in colorectal carcinogenesis. In this cohort of 60 patients, while change in the alpha and beta diversity between supplemented and non-supplemented groups was similar, patients colonized with *Fusobacterium nucleatum* at baseline had a shorter disease-free survival [17]. Vitamin D supplementation resulted in lower post-treatment *F. nucleatum* abundance but women were more likely to harbor *F. nucleatum* post-treatment which highlights the need to consider sex-based differences in microbiota-based treatment studies.

This trial is timely given the growing body of literature focused on dietary-microbiome interactions in cancer risk. Greathouse and colleagues eloquently present what is known about this relationship in their review [18]. Beginning with data on the nutritional impact during cancer treatment, they expand on the role of the microbiome in this relationship and close with precision nutritional therapies and needed future research. One area of this research is to mitigate cancer treatment morbidity/complications through microbiota manipulation. Dr. Secombe and colleagues present their data on mitigating neratinib-induced diarrhea in rats to address this needed translational area of research [19]. Neratinib is an ErbB tyrosine kinase inhibitor used in the adjuvant setting in Her2(+) breast cancer. Diarrhea is the main dose-limiting toxicity of this treatment (as with other chemotherapy and targeted agents) and thus minimizing such toxicities will prevent premature cessation of therapy. This group demonstrated that neratinib treatment resulted in increased diarrhea which was reversed with concomitant neomycin treatment. There was increased inflammation in the distal ileum with neratinib exposure and increased relative abundance of the phylum Proteobacteria. Concomitant treatment with neomycin resulted in a significant increase in the abundance of the genera *Blautia* which may provide an entry point for microbial manipulation measures to limit the toxicity of this medication.

The highlighted studies are just a snapshot of the research presented in this special issue of *Neoplasia* entitled “Implications of the Microbiome in the Development, Progression, Treatment, and Prevention of Cancer” and represent growing areas of microbiome research. Once purely relegated to associative studies, the cancer-microbiome relationship must evolve into causation which will require greater metatranscriptomic analysis, spatial transcriptomics of the tumor microenvironment and associated bacteria, and metabolomic studies with confirmatory translational trials. The importance of this field in the care of cancer patients cannot be overstated and its exponential growth is warranted. Working from humble observations by Dr. Russell, the microbiome-cancer research community must continue to develop its understanding of how microbes help to orchestrate the complex process of carcinogenesis where in many aspects, they are the conductors.

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Declaration of Competing Interest

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CRediT authorship contribution statement

Ryan M. Thomas: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

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