From Clinics to Cosmos: Radiotherapy as a Selector for Stress-Resistant Microbiota

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Radiotherapy (RT) is a cornerstone of cancer treatment, typically delivered over several weeks in daily fractions. While much attention has been paid to its effects on tumor cells and host tissues, less is known about its influence on the human microbiome. Evidence from both clinical studies and space microbiology highlights that microorganisms—whether in the gut or in spacecraft habitats—may adapt more efficiently to environmental stressors than their human hosts.

In a recent review on space microbiomes, Mortazavi et al. [1] argued that chronic exposure to space radiation could select for microbial subpopulations with enhanced resistance to radiation, antibiotics, UV, and desiccation. This adaptation, if unchecked, could pose health risks to astronauts by increasing susceptibility to infections. Although the timescales and conditions differ, a similar principle may apply in the context of clinical RT.

For most microorganisms residing in the human body, therapeutic radiation doses are far below inactivation thresholds—indeed, they may represent only a sub-inhibitory or sub-inactivation dose. Rather than eradicating microbes, such exposures could act as a selective pressure, favoring radiation-tolerant strains or stimulating stress-response pathways. This does not necessarily generate genetically "new" variants within the short span of a 6-week treatment course, but it may shift the ecological balance of the microbiota towards taxa that are more resilient, pro-inflammatory, or pathogenic.

As illustrated in Figure 1, the consequence for patients may be twofold:

- Dysbiosis and immune weakening through loss of beneficial taxa and enrichment of pathobionts.
- Potential acceleration of horizontal gene transfer, raising the possibility of increased antibiotic resistance within the gut ecosystem.

Thus, while RT primarily aims to destroy tumor tissue, it may inadvertently create a microenvironment where the microbiome is under selective evolutionary pressure. This concept deserves systematic exploration, as it may explain observed links between RT-induced dysbiosis, mucosal injury, systemic immune suppression, and patient outcomes.

In summary, lessons from space biology suggest that microorganisms may be "the winners" in adapting to environmental stress. Recognizing

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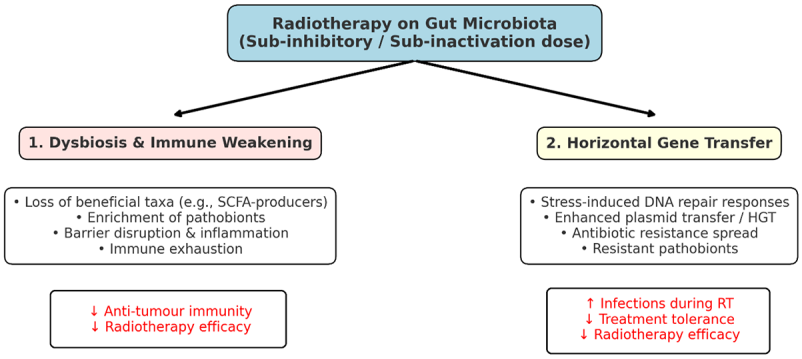

Figure 1: Conceptual model illustrating how Radiotherapy (RT), delivered at sub-inhibitory/sub-inactivation doses for gut microorganisms, may exert selective pressures on the microbiota. Two main pathways are proposed: (1) Dysbiosis and immune weakening through loss of beneficial taxa and enrichment of pathobionts, leading to impaired anti-tumor immunity; and (2) Horizontal Gene Transfer (HGT) and spread of antibiotic resistance, contributing to increased infections and reduced treatment tolerance. Both pathways ultimately converge on reduced efficacy of radiotherapy. (SCFA: Short-Chain Fatty Acids)

that RT doses, though sub-inhibitory for microbes, may shape microbial ecology and adaptation invites new perspectives on supportive care, microbiome monitoring, and therapeutic modulation during cancer treatment.

Furthermore, Rithidech et al. suggested that if apigenin (or related flavonoid compounds) can correct gut dysbiosis induced by space radiation, it may also have the potential to mitigate dysbiosis following radiation therapy [2]. Their results highlighted the potential of dietary apigenin as a countermeasure against radiation-induced gut injury, attributing its benefits to anti-inflammatory effects, reduction of microbiota dysbiosis, and promotion of probiotic bacteria such as Lachnospiraceae, Muribaculaceae, and Bifidobacteriaceae [2].

Although based on limited data, these considerations merit further investigation. Long-term effects during extended missions to Mars or Moon bases should also be evaluated. Difference in the space and terrestrial environments should also be considered including microgravity, radiation environment, atmospheric composition, and electromagnetic background. These effects have not been fully evaluated.

Conflict of Interest

SMJ. Mortazavi and J. Welsh, as the Editorial Board Members, were not involved in the peer-review and decision-making processes for this manuscript.

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