Göteborg, 2019

Towards restoring intestinal health after pelvic radiotherapy

Lessons from dietary fiber intervention in a novel mouse model

Akademisk avhandling

Som för avläggande av medicin doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, Göteborg

Onsdagen den 11 december 2019 Kl. 09:00

av

Piyush Patel

Fakultetsopponent:

Rikard Landberg, Professor

Division of Food and Nutrition Science, Chalmers University of Technology, Sweden

Avhandlingen baseras på följande delarbeten

I. Sjöberg F, Malipatlolla DK, Patel P, Wilderäng U, Kalm M, Steineck G, Bull C. Elastase as a potential biomarker for radiation-induced gut wall injury of the distal bowel in an experimental mouse model. Acta Oncol. 2018;57(8):1025-30.

II. Malipatlolla DK, Patel P, Sjöberg F, Devarakonda S, Kalm M, Angenete E, Lindskog EB, Grandér R, Persson L, Stringer A, Wilderäng U, Swanpalmer J, Kuhn HG, Steineck G, Bull C. Long-term mucosal injury and repair in a murine model of pelvic radiotherapy. Sci Rep. 2019;9(1):13803.

III. Patel P, Malipatlolla DK, Devarakonda S, Bull C, Rascón A, Nyman M, Stringer A, Steineck G, Sjöberg F. Oat bran fiber reduces systemic inflammation in mice subjected to pelvic irradiation. Manuscript.

IV. Patel P, Jin C, Nookaew I, Malipatlolla DK, Devarakonda S, Bull C, Robeson MS, Rascón A, Nyman M, Karlsson N, Wold AE, Steineck G, Sjöberg F. Oat bran fiber protects against pelvic radiation-induced intestinal damage by reducing gut dysbiosis and mucus degradation. Manuscript.

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Lessons from dietary fiber intervention in a novel mouse model

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ABSTRACT

Patients who have cancer in the pelvic region are at risk of developing gastrointestinal symptoms for weeks, months, or even years after receiving radiotherapy. These symptoms are triggered due to unwanted radiation-induced damage to surrounding non-cancerous tissues, resulting in the disruption of normal physiological functions. Worldwide, millions of cancer survivors suffer from reduced bowel health as a consequence of radiotherapy. Quality of life is reduced due to severe gastrointestinal symptoms, such as urgency, fecal leakage, blood and mucus discharge, and excessive production of odorous gases. Our goal was to identify the molecular mechanisms responsible for these symptoms and to prevent its occurrence. To address these issues, we have developed a novel mouse model in which mice were irradiated within a small restricted field that encompasses the distal bowel using a clinical linear accelerator that is used to treat patients. In **Paper I**, biomarkers to identify radiation-induced intestinal injury were studied, and elastase was found to be a good biomarker of radiation-induced injury to the distal bowel. In **Paper II**, the long-term progression of mucosal injury and repair mechanisms after radiotherapy were studied. It was observed that radiation-induced mucosal damage occurs through persistent crypt loss and that repair proceeds through the crypt fission process. In **Papers III** and **IV**, we wanted to investigate whether the advice given to the patients to avoid fiber during radiotherapy is beneficial or detrimental. We found that mice that were fed the fiber-deficient diet and exposed to irradiation had high serum levels of pro-inflammatory cytokines, aberrant mucosal histology, high levels of mucus degradation, low levels of short-chain fatty acids, and signs of gut dysbiosis, as compared to mice that were fed the fiber-rich high oat bran diet and exposed to irradiation. This supports the notion that avoiding fiber during radiotherapy might not be beneficial to patients.

In conclusion, diet plays an important role in modifying the effects of irradiation on intestinal health. A fiber-rich high oat bran diet helps to reduce the harmful effects of radiation and to ameliorate radiation-induced intestinal damage, whereas a fiber-deficient diet exacerbates radiation-induced intestinal damage.

Keywords: Pelvic radiotherapy, radiation-induced gastrointestinal symptoms, oat bran.

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