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Are the solutions to radiotherapy side effects on the gastrointestinal tract right at our doorstep?

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Commentary

From a clinical perspective, radiotherapy is one of the most effective therapeutic swords against malignant diseases available. However, due to its tremendous efficacy, radiotherapy also causes a not insignificant and undesirable collateral damage to the healthy gastrointestinal tract. To reduce these undesirable side effects, physical process optimization with individualized radiation schedules, CT and MRI-assisted optimization of the radiation field, and stereotactic techniques are currently used. Nonetheless, adverse exposure of healthy portions of the bowel cannot be entirely avoided.

The root cause of gastrointestinal radiation toxicity is due to the high basal cell division rate and cell turnover of the healthy intestinal mucosa. This cannot be circumvented due to the mechanism of action of radiation therapy. However, acute side effects on the existing mucosal cells are compounded by a reduction in repair capacity. The current clinical and preclinical research focus is on avoiding this acute cell toxicity by protecting the existing mucosal cells. However, the damage process is currently not well understood.

In a recent study published in *EBioMedicine*, the damage to the tight-junctions by radiotherapy and the prevention of the damage via activation of the MT2 gene by pravastatin is highlighted by Kwak et al. [1]. To evaluate the therapeutic effects of pravastatin, Kwak et al. resorted to detailed modelling in vitro and in vivo. In particular, in vivo, they present data from a minipig model for which the response to radiation injury of the gastrointestinal tract is known to be comparable to that of humans.

The group presents results that pravastatin has a protective effect on the intestinal mucosa by attenuating in vivo radiation-induced enteropathy. In in vitro Caco2 monolayer culture, the group shows that pravastatin can restore intercellular tight-junctions via regulation of metallothionein 2.

Pravastatin is known to reduce radiation toxicity to vessels and that a protective effect on vessels may improve epithelial function [2,3]. However, little is known about the direct effect on epithelial cells. Previously, Wilkinson et al. found that statins enhance tight junction formation and thus attenuate doxorubicin-induced endothelial damage [4]. Here, the direct action and upregulation of the tight junction proteins E-Cad, ZO-1, ZO-2, OCLN, and DSG2, by pravastatin is now demonstrated.

Epithelial dysfunction via disruption of the intercellular junction is well known as a root cause of radiotoxicity, but there is very limited data in this area regarding therapeutic options [5]. When we talk about tight junctions, we also have to talk about the quite complex p38 MAP kinase pathway [6,7]. Kwak et al. nicely add another component here and show that pravastatin probably inhibits p38 MAPK via phosphorylation and, in turn, this regulates tight junction proteins including ZO-1, OCLN and DSG2 in radiation-exposed epithelial cells. In the context of this pathway, an interaction of pravastatin with the transmembrane proteins MT1 and MT2 was additionally shown, which could be further narrowed down to an activation of MT2 by pravastatin via an MT2-deficient mouse and cell model by Kwak et al. However, the basic mechanism of how MT2 expression is activated remains the subject of research and may open up MT2 as another new therapeutic target for radiotherapy-induced enteropathy. However, this further signalling pathway remains to be elucidated.

The clinical implications from this new hypothesis are clear and straightforward. Statins, which include pravastatin, are widely used for other clinical indications, particularly in the older oncology patient population. A short-term retrospective workup of the hypothesis in humans is probably already possible. If the hypothesis is confirmed, a prospective workup must follow; because of the ease of drug availability, the clinical impact on treated patients would be extraordinary. In the clinical context, some retrospective studies of NSCLC and prostate cancer exist showing improved (progression-free) survival for a cohort of patients with statin use [8,9]. In the context of the current results of Kwak et al, this now provides a much broader scope for interpretation. Both clinically and preclinically, exciting times are coming with new answers.

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Contributors

CB conceived and wrote this invited Commentary.

Declaration of Competing Interest

The author reports personal fees from Janssen Pharma, outside the submitted work.

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