CANCER

Preventing collateral damage

In pigs, nitrate supplements can protect salivary glands from the damage caused by radiation therapy to the head and neck.

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Most patients with head and neck cancer will receive radiation therapy in order to kill or shrink their tumor (Alterio et al., 2019). During treatment, physicians try to minimize damage to surrounding, healthy tissues, but off-target doses often harm and kill the sensitive ‘serous acinar cells’ in the salivary parotid gland (Figure 1A). As a result, many patients go on to produce less saliva and develop a persistent dry mouth, also known as xerostomia. This is not a benign condition: people may experience loss of taste, difficulty chewing, swallowing or speaking and, in the long term, tooth and gum decay that can lead to malnutrition (Jensen et al., 2019).

Few interventions exist to stop this side effect from emerging, aside from technical refinements that limit the exposure of the glands to radiation (Mercadante et al., 2021). Now, in eLife, Songlin Wang and colleagues at Capital Medical University – including Xiaoyu Feng and Zhifang Wu as joint first authors – report a remarkably simple measure that may protect salivary glands during radiation therapy (Feng et al., 2021).

Related research article Feng X, Wu Z, Xu J, Xu Y, Zhao B, Pang B, Qu X, Hu L, Hu L, Fan Z, Jin L, Xia D, Chang S, Wang J, Zhang C, Wang S. 2021. Dietary nitrate supplementation prevents radiotherapy-induced xerostomia. eLife 10:e70710. doi: eLife.70710

In the body, these glands are an important component of the nitrate cycle, taking up about 25% of the inorganic nitrate present in the blood, concentrating it and then secreting it into the saliva (Lundberg et al., 2018). This nutrient, abundant in leafy greens and many fruits, was once reviled for potentially causing cancer but it is now viewed as a normal component of a healthy diet. It can even help to boost the regeneration of certain heart cells (Lundberg et al., 2018; Marino et al., 2021).

Feng et al. used miniature pigs – whose salivary glands are structurally similar to those of humans – to investigate whether nitrate could help protect against xerostomia after radiation therapy. Animals that were fed daily doses of inorganic nitrate before treatment did not experience a sharp drop in saliva production, and they recovered 80% of their salivary flow within two years.

These benefits were both dose- and time-dependent: higher amounts of supplementary nitrate led to better salivary gland function, but administering the nutrients for the first time two months after treatment yielded minimal results. In the laboratory, adding inorganic nitrate to cells derived from human parotid tissues revealed a similar radioprotective effect. Taken together, these results strongly support supplementing patient’s diets with nitrate to prevent xerostomia.

Exactly how nitrate can protect cells against radiation is not fully understood, but it may involve sialin, a transport protein that helps to usher the nutrient inside serous acinar cells. Feng et al. showed that radiation caused the levels of sialin to rapidly fall. Adding nitrate before treatment, however, boosted the level of sialin, and therefore the amount of the nutrient inside cells. Additional experiments suggest that nitrate then increases the production of sialin, creating a positive feedback loop that activates the EGFR-AKT-MAPK pathway (Figure 1B). This biochemical circuit is known to stimulate cell growth and block programmed cell death (Seshacharyulu...
et al., 2012). The production of sialin in response to nitrate appeared to be the critical trigger for EGFR activation, which may explain why supplementation was only effective if administered before radiation therapy.

Extrapolating from animal and cell-based models to humans is always uncertain (Mak et al., 2014). Perhaps the most exciting aspect of the work by Feng et al. is that its main conclusion is easy to test, through randomized clinical trials that monitor salivary function (and potentially nitrate levels) before, during and after radiation therapy. This will ultimately help to determine whether nitrate supplementation could offer a low-tech solution to a high-tech problem. If the stunning results presented by Feng et al. translate to humans, this approach may have a major impact on cancer patients experiencing xerostomia.

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References

Alterio D, Marvaso G, Ferrari A, Volpe S, Orecchia R, Jereczek-Fossa BA. 2019. Modern radiotherapy for head and neck cancer. Seminars in Oncology 46:233–245. DOI: https://doi.org/10.1053/j.seminoncol.2019.07.002, PMID: 31378376

Feng X, Wu Z, Xu J, Xu Y, Zhao B, Pang B, Qu X, Hu L, Hu L, Fan Z, Jin L, Xia D, Chang S, Wang J, Zhang C, Wang S. 2021. Dietary nitrate supplementation prevents radiotherapy-induced xerostomia. eLife 10:
e70710. DOI: https://doi.org/10.7554/eLife.70710, PMID: 34581269
Jensen SB, Vissink A, Limesand KH, Reyland ME. 2019. Salivary gland hypofunction and xerostomia in head and neck radiation patients. JNCI Monographs 2019: lgz016. DOI: https://doi.org/10.1093/jncimonographs/lgz016, PMID: 31425600
Lundberg JO, Carlström M, Weitzberg E. 2018. Metabolic effects of dietary nitrate in health and disease. Cell Metabolism 28: 9–22. DOI: https://doi.org/10.1016/j.cmet.2018.06.007, PMID: 29972800
Mak IW, Evaniew N, Ghert M. 2014. Lost in translation: animal models and clinical trials in cancer treatment. American Journal of Translational Research 6: 114–118 PMID: 24489990.,
Marino F, Scalise M, Cianflone E, Salerno L, Cappetta D, Salerno N, De Angelis A, Torella D, Urbanek K. 2021. Physical exercise and cardiac repair: the potential role of nitric oxide in boosting stem cell regenerative biology. Antioxidants 10: 1002. DOI: https://doi.org/10.3390/antiox10071002, PMID: 34201562
Mercadante V, Jensen SB, Smith DK, Bohlke K, Bauman J, Brennan MT, Coppes RP, Jessen N, Malhotra NK, Murphy B, Rosenthal DJ, Vissink A, Wu J, Saunders DP, Peterson DE. 2021. Salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies: ISOO/MASCC/ASCO Guideline. Journal of Clinical Oncology 39: 2825–2843. DOI: https://doi.org/10.1200/JCO.21.01208, PMID: 34283635
Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK, Batra SK. 2012. Targeting the EGFR signaling pathway in cancer therapy. Expert Opinion on Therapeutic Targets 16: 15–31. DOI: https://doi.org/10.1517/14728222.2011.648617, PMID: 22239438