Intestinal regeneration: Lessons from organoid research

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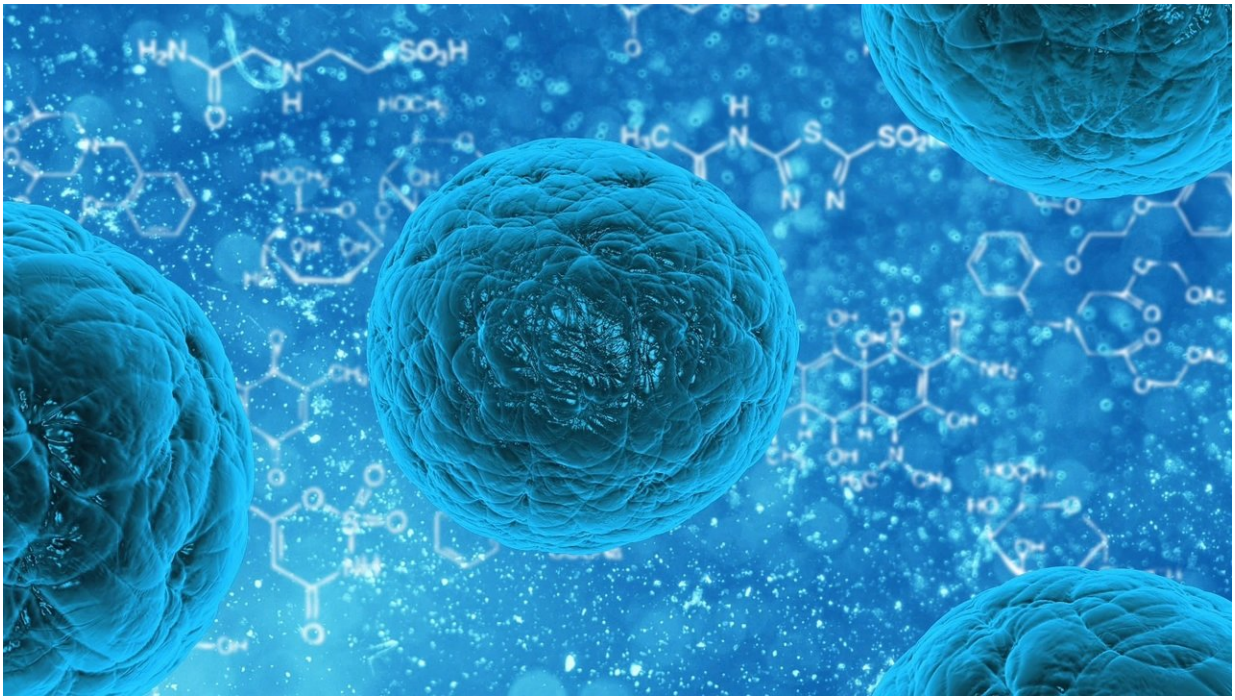

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The last decade has seen a boom in the field of organoids, miniature organs grown from stem cells in vitro. These systems recapitulate the cell type composition and numerous functions of parent organs—such as brain, kidney, intestine or lung—and are perfectly suited for experimental manipulations, making them invaluable tools for researchers worldwide.

Organoids from the intestine—the fastest renewing tissue in mammals—recapitulate not only the structure of intestinal epithelium but also its ability to regenerate following damage. Intestinal organoids can develop from a single cell, driven by the intrinsic capacity of a cell to undergo a regenerative process, building a complicated hierarchical structure through self-organization. However, the factors that drive and regulate this process are not well understood.

Researchers from the group of Prisca Liberali set out to understand intestinal regeneration by mapping the functional genetic interactions regulating this process. For this, they established an image-based phenotypic screening platform, profiling over 400,000 organoids treated with a library of compounds to assess which compounds affect the organoids. They then classified every organoid by phenotype, generating a unique "phenotypic fingerprint" for each of the 3,000 compounds screened.

This unprecedented dataset allowed the researchers to identify 230 genes involved in organoid development and map functional genetic interactions between them. Hits of the screen included an inhibitor of the retinoic acid signaling pathway that promoted the regenerative phenotype in organoids, confirmed by altered gene expression and cell type composition, and ultimately in vivo: mice with radiation-induced intestinal damage recovered better when treated with the compound, showing improved tissue regeneration and reduced weight loss.

"This study represents an incredible technical tour de force, and the screening platform we developed can be applied widely, to many systems," says group leader Prisca Liberali. "We established the first map of functional interactions in intestinal organoid development. Furthermore, we identified a compound that selectively affects regenerative cells, prolonging the time cells spend in a regenerative state without causing uncontrolled cell division. We believe that our findings

pave the way for novel therapies to promote regeneration and recovery of the intestinal epithelium following acute damage, for instance in cancer patients receiving chemo- or radiation therapy."

More information: Ilya Lukonin et al. Phenotypic landscape of intestinal organoid regeneration, *Nature* (2020). DOI: 10.1038/s41586-020-2776-9

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