HORIZON 2020

The role of Ubiquitin System on the homeostatic control of stem cell maintenance and differentiation in crypt stem cells

Results in Brief

3D organoids provide insight into stem cell biology

Constant exposure to environmental hazards causes small intestine and skin epidermis to self-renew at an intriguingly high pace. Understanding the mechanism underlying self-renewal in these mammalian tissues is paramount for comprehending excessive cell proliferation known as hyperplasia.

HEALTH

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Tissue homeostasis is tightly controlled and perturbation can cause disease or cancer. Under normal conditions, tissue endogenous stem cells receive signals that allow them to self-renew or differentiate to maintain tissue steady state. Although transcriptional regulation is paramount for controlling stem cell numbers, little is known about the role of post-transcriptional and post-translational modifications such as RNA methylation and protein ubiquitination in stem cell biology.

Intestinal organoids: a model system for studying stem cells

Undertaken with the support of the Marie Curie programme, the EU-funded

IntestineUb project investigated various aspects of stem cell biology such as multipotency, maintenance and differentiation in 3D primary intestinal organoids. As the primary investigator of the project, Dr Ya-Lin Huang explains, “primary intestinal organoids comprise a powerful model in vitro system since they recapitulate the in vivo epithelium organisation and at the same time are amenable to essentially all experimental technologies.”

Emphasis was given to enzymes implicated in RNA methylation such as the Nop2/SUN (NSUN) family of RNA methyltransferases, and deubiquitinating enzymes (DUBs) known for their role in protein degradation. The aim was to characterise the expression pattern of these enzymes and loss-of-function phenotypes in stem cells and identify those required for stem cell number regulation.

Using the CRISPR/Cas9 technology, researchers performed loss-of-function studies in intestinal organoids and skin keratinocytes, targeting various NSUN and DUB genes. Extensive genetic engineering alongside in vitro assays helped examine the effect of candidate NSUNs and DUBs in known signalling pathways involved in homeostatic control.

In another part of the IntestineUb project, scientists investigated the role of the Wnt signalling pathway in intestinal stem cell proliferation. Although the Wnt pathway has been extensively studied in various types of stem cells, most reports address the effects of Wnt signalling through transcriptional activation by β-catenin. IntestineUb focused on Wnt/STOP signalling, which acts independently of β-catenin and transcription, and regulates protein abundance through degradation. Researchers validated the function of Wnt/STOP signalling in intestinal organoids and discovered that it targeted DUBs.

Towards tissue regeneration and cancer therapy

Undoubtedly, dissecting stem cell regulatory pathways is fundamental to understanding how perturbed homeostasis causes diseases and cancer. Despite decades of research, very little is known about the function of NSUN and DUB enzymes in epithelial stem cell homeostasis. Dr Huang emphasises that “the originality and innovative nature of the IntestineUb project lies in the combination of the biochemical analysis of NSUNs and DUBs with the physiology of epithelial stem cell homeostasis.”

The results of the study provide unprecedented knowledge on stem cell biology and lay the foundation for the future investigation of NSUN and DUB enzymes to find therapeutic targets. Future plans mainly involve the elucidation of the physiological role of key NSUN and DUB candidate genes in vivo using knockout mouse models.

From a clinical perspective, IntestineUb findings could fuel research into inhibitors

that modulate stem cell function and potentially attenuate hyperplasia. Furthermore, according to Dr Huang “insight into the biology and properties of tissue stem cells holds the key to regenerative therapies.”

Keywords

IntestineUb, stem cell, DUBs, NSUNs, intestinal organoid, enzyme, homeostasis, hyperplasia, Wnt signalling, in vitro, assay, CRISPR/Cas9

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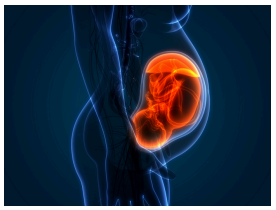

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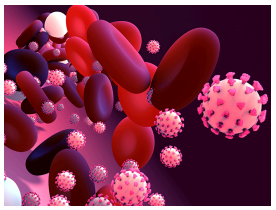

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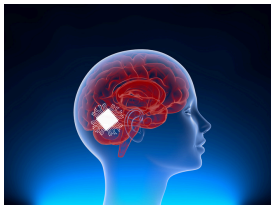

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IntestineUb

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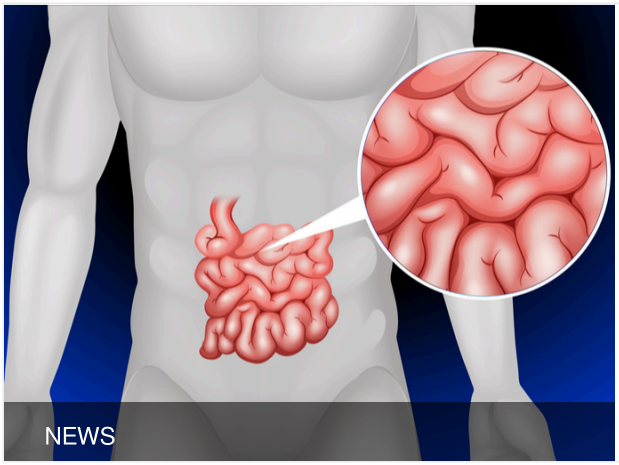

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