EXPERIMENTAL MODEL

Modelling immune–microbe interaction in 3D intestinal culture

A new 3D microfluidic organ culture system enables characterization of intestinal immune responses to gut microbiota under tightly controlled conditions. Using the approach, researchers have uncovered novel interactions between specific microbial species and host neuronal signalling.

As appreciation of the importance of host–microorganism crosstalk has grown, so has the demand for informative model systems that recapitulate these interactions. However, existing models are imperfect. Organoid culture systems, for instance, enable modelling of the epithelium and tight experimental control, yet lack features of whole tissue. “One missing component of some organoid systems is a functional nervous system,” explains author Isaac Chiu. Conversely, animal models provide physiologically relevant intestinal tissue, but control of experimental conditions is limited.

To address the deficits of these models, the researchers devised a system to culture

mouse intestine *ex vivo*. The ends of excised intestinal segments were connected to input and output ports, enabling the controlled delivery of molecules and microorganisms to the lumen. Intestinal segments were semi-submerged in media, which was replenished by another pump system.

Cultured tissue was viable for several days; as some epithelial degradation was observed after 24 h, the researchers only conducted experiments within this timeframe. Numerous experiments showed preservation of intestinal functions in culture, including intestinal epithelial cell proliferation, epithelial barrier integrity, normal enteric nervous system structure and physiological immune cell populations.

Next, the investigators demonstrated that the culture system could support the growth of gut microbiota. By introducing species eliciting host responses (segmented filamentous bacteria, which induce T helper 17 cells, and a broad panel of

bacteria that induce ROR γ^+ regulatory T (T_{reg}) cells), Chiu and colleagues were able to characterize the early transcriptional response in host tissue.

Notably, they found that neuron-related genes, including those known to be enriched in nociceptor neurons, were repressed by microorganisms inducing ROR γ^+ T_{reg} cells, indicating neural–immune–microbial interaction. Culture of primary sensory neurons with a species inducing ROR γ^+ T_{reg} cells altered neuronal firing rate, as did culture of neurons with material secreted by inducing microorganisms. “Finding microorganisms and how they regulate neuronal responses could have important implications for gastrointestinal motility and pain,” stresses Chiu.

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