

The logo for the EMBO | EMBL Symposium. It features the text "EMBO | EMBL" in white, followed by a circular icon composed of a grid of small dots, and then the word "Symposium" in white. The background of the entire poster is a dark, abstract image showing a cross-section of a developing organoid with various colored cells (green, purple, red) and a blue and white striped structure on the right.

EMBO | EMBL Symposium

Organoids

Modelling Organ Development
and Disease in 3D Culture

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Tumor organoid models for studying extracellular vesicles

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Extracellular vesicles (EV) are membrane-surrounded „bubbles” that transfer biologically active molecules (e.g. lipids, proteins, RNAs) from the releasing to target cells, thus representing a novel way of intercellular communication. Importantly, EVs hold a great promise for cancer diagnostics as well. Circulating EVs are a heterogenous population with different cellular origin. Most studies have so far used 2D cell cultures in EV research which do not properly model the in vivo situation. Here we show that EVs produced by organoids from colorectal cancer (CRC) or pancreatic ductal adenocarcinoma (PDAC) patients can be detected in 3D culture supernatant by antibody-coated beads. Unlike 2D cultures, the distribution of EVs is shifted to the smaller size range in 3D culture medium. EVs from 3D cultures carry biologically important molecules, such as miRNAs. Interestingly, EV release from organoids depends on the mutational status of tumor-driver genes in both cancer types, furthermore, critical factors modify the intensity of EV secretion. Surprisingly, we observed a massive EV secretion not only from PDAC and CRC tumor cells and organoids, but also from stromal cells, suggesting that a substantial proportion of tumor-derived EVs in the body fluids of PDAC patients is of stromal origin. Collectively, our results show that the organoid technology is a suitable model system to study EV functions in different cancer types.

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WNT-5A/5B signaling represses functional responses in lung epithelial progenitors

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COPD represents a worldwide concern with high morbidity and mortality, and is believed to be driven in part by accelerated ageing of the lung. Although several studies indicate a role for non-canonical WNT signaling, in ageing and COPD, the precise impact of non-canonical WNT signaling on lung repair remains poorly understood. We hypothesized that WNT-5A/5B might impact on alveolar epithelial repair. Lungs were harvested for precision-cut lung slices (PCLS) or the generation of lung organoids. PCLS were treated with WNT-5A or WNT-5B (500 ng/mL) or vehicle control. Lung organoids were established by co-culturing epithelial cells (EpCAM+/CD45-/CD31-) with CCL206 fibroblasts in Matrigel. The gene expression levels of WNT-5A and WNT-5B were increased in PCLS from aged WT mice and their expression correlated with the senescence marker p16. In PCLS from young WT mice, WNT-5A treatment had no effect on gene expression of the type I/II epithelial cell markers Aqp5/Sftpc; however, WNT-5B treatment significantly decreased gene expression of Aqp5 and Sftpc. In addition, WNT-5B significantly decreased expression of the canonical WNT target gene, Axin2. The number of organoids visible 7 days after culture was significantly decreased by WNT-5A and WNT-5B. WNT-5A significantly decreased the number of airway type organoids, whereas WNT-5B selectively repressed alveolar type organoid formation. Immunofluorescence studies confirmed that numbers of acetylated- α tubulin+ organoids were significantly decreased by both WNT-5A and WNT-5B, however, numbers of SPC+ organoids were significantly decreased by WNT-5B. Neither WNT-5A nor WNT-5B stimulation affected the size of lung organoids measured on day -14. Non-canonical WNT signaling is correlated with ageing. Thus, the non-canonical WNT ligands WNT-5A and WNT-5B repress gene expression of alveolar epithelial cell markers in lung slices, and functionally inhibit lung organoid formation. We speculate that such a mechanism may contribute to defective alveolar repair in ageing and COPD.