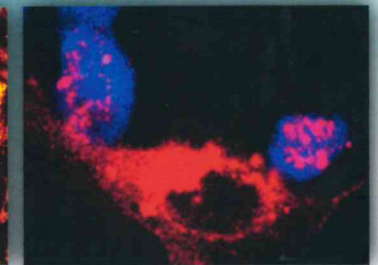
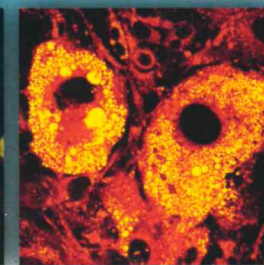
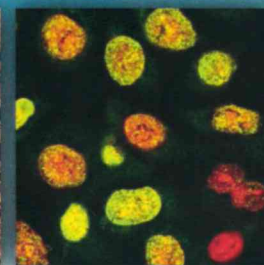
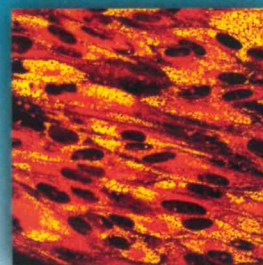
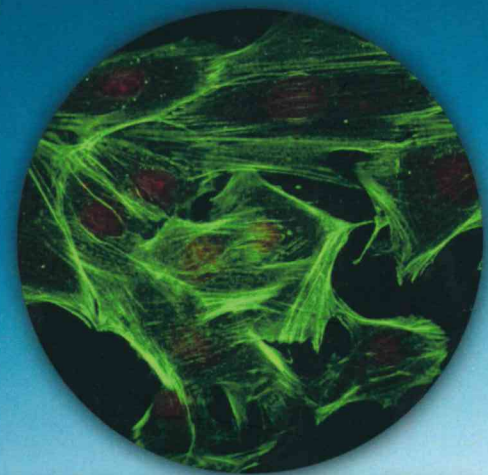
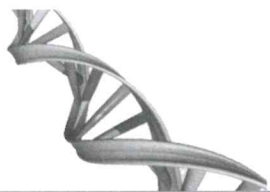


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Pancreatic cancer patient-derived 3D organoids to analyze extracellular vesicles

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most dangerous cancers with a 5-year survival rate of less than 8%. Despite the intensive research efforts, there is only a slow progress in the early diagnosis and treatment efficiency of this disease. PDAC consists of not only tumor cells, but also of a high amount of stroma, containing mostly cancer-associated fibroblasts (CAF). The intensive communication between the heterogeneous cell populations evolves the tumor niche and contributes to tumor progression.

Extracellular vesicles (EV) are membrane-surrounded particles that transfer biologically active molecules (e.g. lipids, proteins, RNAs) from the releasing to target cells in a pre-packaged form, thus representing a novel way of intercellular communication. Importantly, since tumor-derived EVs transport their tumor-specific cargo in a protected way in the body fluids, they hold a great promise for early tumor detection. However, the potential use of EVs as biomarkers is largely hindered by the lack of proper methods to study their release and cargo composition.

Most studies have so far used 2D cell cultures in EV research which do not properly model the *in vivo* situation. Here we prove that 3D pancreas-derived organoid technology is a proper method to study EVs. Interestingly, EV release from PDAC cell lines and pancreas organoids depends on the mutational status of tumor-driver genes. Surprisingly, we observed a massive EV secretion not only from PDAC 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. Furthermore, we show that EVs released from 3D and 2D cultures differ in their molecular cargo, highlighting the importance of model systems when analysing EV molecular composition.

Collectively, our results show that the 3D organoid technology is a promising model system to study EV functions in PDAC for diagnostic or therapeutic purposes.



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Keywords: PDAC, pancreas, adenocarcinoma, extracellular vesicles, organoid technology

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The role of endogenous retroelements in neural aging in the canine model of human senescence

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An increasing body of experimental evidence suggests that age-related mobilization of endogenous transposable elements may be at least partly responsible for the genomic instability which will eventually lead to cellular senescence and aging of model organisms from yeast to mice. The same mechanism might be present in aging human tissues, as genomic hypomethylation of Alu and LINE-1 (long interspersed nuclear element 1) retrotransposon sites were indicated in aging cohort studies. Although direct evidence about retrotransposon mobilization in human tissues have been limited so far, recent findings suggested that retrotransposon mobilization may be induced by tau pathology in patients with neurodegeneration. Dogs have been proposed as natural models of human age-related dementia, as they develop Canine Cognitive Dysfunction Syndrome (CCD), which shares many hallmarks with early stage Alzheimer's disease. Thus, the identification of retrotransposon mobilization in canine brain samples could help scientists to clarify the contribution of retroelements to dementia. So far, somatic activation of LINE-1 retrotransposons has not been investigated in dog brains. A main limitation is the inaccessibility of post mortem brain tissue from aged or demented dogs.

In our study, we used brain cortical samples from our new initiative, the Canine Brain Tissue Bank (CBTB), to measure expression of the canine LINE-1 open reading frame 2 (ORF2), which is highly conserved between dogs and humans. The first step was the collection of suitable sample material. Samples were provided from the bodies of pet dogs which had been previously donated by their owners with consent of the veterinarian who euthanized the animal for justified medical reasons. The tissue pieces intended for RNA and protein isolation were stabilized in appropriate buffers immediately after removal from the body, within 4 hours post mortem.

Our preliminary results showed that ORF2 was present as translated protein in