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Pancreatic stellate cell heterogeneity in cancer

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Introduction: Paracrine interactions between pancreatic stellate cells (PSCs) and tumor cells play key roles in pancreatic cancer tumorigenesis. However attempts to therapeutically target the PSCs have led to contradictory results, raising the possibility of diverse pathophysiological roles of these cells.

Aims: The aim of this project is to gain a deeper understanding of the functional heterogeneity found in PSCs.

Materials & methods: We have developed an organotypic co-culture system that allows us to study the interactions between tumor-derived organoids and PSCs in a three-dimensional matrix (Matrigel). Murine and human tissues have been used to validate our findings.

Results: PSCs embedded in Matrigel acquire a quiescent phenotype, but become highly proliferative when co-cultured with tumor cells and differentiate into two distinct subtypes showing different phenotypic features. PSCs found in direct contact with tumor cells express smooth muscle actin (SMA), while PSCs that are more distant from the tumor cells show low SMA expression and gain a secretory phenotype. The secreted factors from this subtype of PSCs can activate certain pathways in tumor organoids important for proliferation and survival. We also show that these two subtypes are mutually exclusive and can both be found *in vivo* with similar spacial distribution as seen in the co-culture system.

Conclusion: We have identified two subtypes of PSCs present in pancreatic cancer with potentially different pathophysiological functions. We believe that the outcome of trials targeting the PSCs will depend on which subtype that is preferentially affected by the treatment.

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Epigenetic alterations mediated by Ring1b are crucial for acinar-to-ductal metaplasia and pancreatic carcinogenesis

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Introduction: Besides defined genetic mutations, a deregulation of epigenetic remodelers highly contributes to pancreatic cancer formation in a setting of inflammatory acinar-to-ductal metaplasia (ADM). By analyzing an in-vitro carcinogenesis model, we have already shown that the epigenetic histone modifier Ring1b is reactivated during tumor development, accounting for the transcriptional silencing of the acinar cell fate genes *Ptf1a* and *Rbpjl.*

Aims: To proof that epigenetic changes catalyzed by Ring1b are of importance for ADM formation and pancreatic tumor progression, we established an inducible Cre-mediated conditional Ring1b knockout mouse model as well as Ring1b deficient tumor cells.

Materials & methods: Ring1b KO mice were subjected to the cerulein-induced regeneration model and a $Kras^{G12D}$-dependent tumorigenesis. Tissue was analyzed with the aid of immunohistochemistry, Western Blot, chromatin immunoprecipitation (ChIP), qRT-PCR and RNA microarray analysis. Additionally, Ring1b was depleted in tumor cells via CRISPR/Cas9 and cells were functionally analyzed.

Results: Conditional Ring1b knockout mice undergoing cerulein-induced pancreatitis barely exhibited any tissue damage, ADMs and inflammation. Moreover, the formation of early precursor lesions was strongly impaired in Ring1b depleted $Kras^{G12D}$ mice. Here, expression analyses revealed elevated expression levels of differentiation genes, such as *Rbpjl*, whereas the expression of the progenitor genes *Rbpj* and *Sox9* was decreased in the knockout mice. After orthotopic injection into the pancreases of wildtype mice, Ring1b depleted tumor cells formed none to very small tumors. Moreover, Ring1b depleted tumor cells were more sensitive to gemcitabine.

Conclusion: Epigenetic changes mediated by Ring1b are an important prerequisite for acinar-to-ductal-metaplasia, pancreatic tumor development and progression.

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Chronic pancreatitis in primary care in Ireland: The management of an orphan disease

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Introduction: There are no data regarding the incidence, prevalence, hospitalisation, aetiology or management of chronic pancreatitis(CP) in Ireland, nor have the experiences and insights of frontline clinicians been sought.

Aims: We devised a survey for use with general practitioners(GP), and have used it on a sample equivalent to 20% of GPs nationally, to determine national and regional trends in CP management in the primary care setting, and to obtain their insights, experiences, and concerns on the management of CP, and the proposed development of a national CP registry

Patients & methods: 23-question survey was twice posted to 563 randomly selected GPs. The survey was subject to pilot (n=20). Data were analysed using SPSS.

Results: Response rate was 69%. Most respondents(62%) were male and 88% had >8years GP experience. Almost all(96%) were unaware of any national/international consensus guidelines for CP management. Whilst most(79%) of GPs reported having CP pateints currently in their care, almost half(49%) have no access to MDT. Forty-three percent of GPs indicated a disease registry would be useful, however only 26% felt it would be actively utilised. Two in five GPs indicated they were “unhappy” with the ongoing level of care

Conclusion: Deficits exist in guideline knowledge, MDT support and management of CP patients in the primary care setting in Ireland. Many GPs were unsure if a disease registry would be utilised by healthcare professionals, and most were unhappy with the prospect of ongoing care of CP patients. It is evident from the study that CP is not being managed at present as a chronic disease.

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Vascular enhancement pattern of mass in computed tomography may predict chemo-responsiveness in advanced pancreatic cancer

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Introduction: Chemo-responsiveness in pancreatic cancer with liver metastasis may be different among the patients.

Aims: The purpose of this study is to assess vascular enhancement of pancreatic ductal adenocarcinoma with liver metastasis and to analyze the correlation between enhancement and chemo-responsiveness