Editorial

The microbiome as a potential diagnostic biomarker for pancreatic ductal adenocarcinoma (PDAC)

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Pancreatic ductal adenocarcinoma (PDAC) is a major cause of cancer-related death worldwide. Despite recent advances in treatment options, prognosis remains poor, and data estimates from the United States (US) show that PDAC will surpass colorectal cancer to become the second most common cause of cancer-related death by 2040 (1). Surgery followed by adjuvant chemotherapy is the only potentially curative treatment option for patients with PDAC; however, the majority present with advanced stage, non-resectable disease. Early diagnosis could improve the dismal prognosis for this patient group, but this remains challenging due to numerous factors including a lack of approved biomarkers and screening programmes, and non-specificity or late presentation of symptoms.

The development of cost-effective, high-throughput next-generation sequencing (NGS) technology has resulted in a substantial increase in studies investigating the relationship between the microbiome and cancer. To date, studies have reported on the oral and/or gut microbiome and subsequent risk of PDAC (2,3), as well as exploring the association between intra-tumoural microbiota and survival outcomes in patients with resected PDAC (4). Despite the growing body of evidence supporting the role of the microbiome in the diagnosis and prognosis of pancreatic cancer (5), many questions are unanswered, and both clinical application and therapeutic utilisation of the microbiome remain investigational.

In their recent publication, Kartal *et al.* reported on the faecal and salivary microbiota of 57 newly diagnosed, treatment-naïve patients with PDAC, 29 patients with chronic pancreatitis (CP) and 50 matched controls (6), with the aim of identifying potential diagnostic biomarkers. The faecal microbiome composition of patients with PDAC differed significantly from controls ($P \leq 0.0001$) and patients with CP ($P=0.003$). Furthermore, differential abundance testing of the faecal microbiota revealed nine species that were significantly differentially abundant in either group (PDAC cases versus controls). *Veillonella atypica*, *Alloscardovia omnicolens*, and *Fusobacterium nucleatum/hwasookii* were enriched in the faeces of PDAC cases, with a further six species noted to be enriched in controls (and depleted in PDAC cases). In contrast, no significant differences in overall composition were identified in the salivary microbiome.

To further explore these findings, Kartal *et al.* developed a microbiome-based statistical model incorporating 27 faecal microbial species (6). The model discriminated between patients with PDAC and controls with high accuracy [area under the receiver operating characteristic (AUROC) =0.84] and with consistent accuracy across early and late disease stages. Interestingly, combining serum carbohydrate antigen (CA) 19-9 levels with the faecal microbial classifiers increased the accuracy of the model (AUROC =0.94). However, CA19-9 levels were only available for a subset

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of participants (33/50 controls and 44/57 PDAC cases). A similar model was developed based on salivary microbial species, but no robust signature was detected (AUROC =0.48). Furthermore, a second model confined to PDAC-enriched faecal species only was developed; this performed with slightly less accuracy than the first model (AUROC =0.71), but the accuracy improved when combined with CA19-9 levels (AUROC =0.89). This data proves that combining biomarkers (e.g., CA19-9) with faecal microbial classifiers can improve non-invasive detection of PDAC, and future studies should continue to explore this approach. It is however important to highlight that approximately 10% of patients are unable to synthesise CA19-9 due to a lack of Lewis antigen (7), and this may reduce the accuracy of combined models for PDAC detection in this cohort.

Crucially, the prediction accuracy of both faecal microbiota-based models was tested in two validation scenarios: firstly, in an independent study population from Germany (44 patients with PDAC, 32 matched controls) and secondly, against external metagenomic datasets (25 studies, n=5,792) on various diseases. Both models had high prediction accuracy in the German validation population, and the second model (confined to PDAC-enriched species only) was highly disease-specific when validated against the external metagenomic datasets.

This comprehensive prospective study demonstrates the potential of the faecal microbiome as a tool for early diagnosis of PDAC. The authors have carefully considered potential confounding factors (inclusive of 26 demographic and clinical variables); none of which were individually associated with the faecal microbial species included in the microbiome-based statistical model. This suggests the faecal microbiota signature could be independently predictive of PDAC, and will require validation in future studies. It is also important to recognise that technical variation has an influence on data outputs in microbiome studies, and reassuringly Kartal *et al.* ensured the same protocol for sample collection, storage, and processing was used for the study cohort and the German validation cohort. Nevertheless, technical variation may have had an impact on the data outputs relating to the second validation scenario, which included the metagenomic datasets from 25 external studies. Geographical variation in gut microbiota is also well documented (8), and must be considered when comparing inter-study microbiome data. In this case, Kartal *et al.* incorporated external datasets from studies across the globe (including Europe, Asia and the US), thus strengthening the validity of their faecal microbiota-based model.

The authors also analysed 23 PDAC tumour biopsies (with matched healthy tissue from 20 participants), and found that *Lactobacillus* spp, *Akkermansia muciniphila*, and *Bacteroides* spp were significantly enriched in PDAC tissue (P<0.006) (6). Interestingly, on comparison of the presence of different genera in all four studied body sites (faeces, saliva, PDAC tissue, and adjacent healthy tissue); they identified overlap between the amplicon data of salivary, faecal and PDAC tissue. The oral-gut microbiome axis in gastrointestinal disease and cancer has been described in previous studies (9); however, this new data also poses interesting questions about a potential oral-gut-PDAC microbiome axis. Inter-organ microbial communication may also be important in other hepatopancreaticobiliary (HPB) cancers, with an increasing focus on the potential role of the gut-liver microbial axis (10). Integration of oral, gut, and tissue microbiome data is required to improve understanding of the potential role of the oral-gut microbiome in carcinogenesis, and should be encouraged in future studies.

The microbiome offers potential as a tool for early diagnosis of PDAC, prognostication, or even as a future therapeutic target. Studies in other cancer types have also explored the role of the microbiome in modulating treatment response (11-13), and similar studies should be encouraged in patients with PDAC. Although there have been advances within this field of research, it is important to recognise that, at present; the marked heterogeneity of studies limits the comparability of PDAC-associated microbiome signatures. For example, a previous prospective case-control study demonstrated that carriage of specific oral microbes was associated with subsequent risk of pancreatic cancer (2); however, Kartal *et al.* did not observe any significant differences in oral microbiome composition between PDAC cases and controls. Additionally, Kartal and colleagues confirm the presence of PDAC-associated intra-tumoural microbiota; however, no similarities in composition can be drawn with those reported by Riquelme *et al.* (4). Adoption of the 'Strengthening The Organisation and Reporting of Microbiome Studies' (STORMS) checklist (14) is a step towards tackling inter-study heterogeneity, and will hopefully improve the standard of reporting within microbiome research across the board, and allow thorough comparative analysis of published results, including meta analyses.

In summary, the microbiome is a challenging, but promising, field of research and warrants further investigation.

Well-designed prospective preclinical and clinical studies exploring the association between the microbiome and PDAC should be encouraged, and future studies should focus not only on the role of the microbiome in carcinogenesis, but also explore the potential impact of the microbiome on patient treatment and survival outcomes.

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