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METAGENOMIC AND METABOLOMIC ANALYSES REVEAL DISTINCT STAGE-SPECIFIC PHENOTYPES OF THE GUT MICROBIOTA IN COLORECTAL CANCER

Several analyses have been conducted to identify factors, which might promote colorectal cancer (CRC) development. As the immune system appeared as a fundamental actor in the scene, a growing interest was focusing on the microbioma. Alterations in the gut ecosystem have been implicated in the changes in human health and disease. Intestinal metabolites have also been recognised and associated with CRC.[1–3] In a relevant article recently published in *Nature Medicine*[4] by several academic institutions from Japan, a wide metagenomic and metabolomic analysis collecting data from more than 500 subjects to better characterise the relation between intestinal flora and the development of CRC was performed. Patients were divided into nine different subgroups according to colonoscopy and histological findings, as well as for risk factors such as smoking, alcohol assumption and body mass index. Human genome content was analysed and it was significantly higher in various stages of CRC than controls with Bacteroides and Prevotella being the major contributors to human gut enterotypes. Principal component analysis (PCA) identified the two most variable clusters in all subjects and in 251 healthy controls. The PCA showed large variation in dihydrouracil and urea in addition to propionate and butyrate in the population. Despite this, none of the stages, tumour locations or genders was associated with variation in metabolite profiles. Nevertheless, compared with the healthy controls, microbiome was highly distinct across stages. A number of species in the phyla Firmicutes, Fusobacteria and Bacteroidetes was increasing with the degree of malignancy and a large number of species were elevated only when multiple polyps were found. Two patterns of significant species elevation were highlighted. The first increased across early to later stages, whereas the second was elevated only in the early stages. In addition, new species associated with CRC were identified. In total, 65 metabolites showed significant differences in at least one of the stages compared with healthy controls.

This publication shows that microbiome and metabolome shift in multiple polyposis and T0/Tis in addition to the more advanced stages. Two patterns of species elevation were found: the first consisted of a continuous increase from early stages onwards, whereas the other showed elevation only in early stages. Nevertheless, it was no longer possible to clarify any potential microbial involvement in stages prior to the formation of adenomas and more detailed causalities between microbiome and/or metabolome and tumours, so that a longitudinal investigation is needed. In addition, clarification of relationships between the gut microbiome and tumour molecular characteristics in individual patients with CRC will be necessary to understand the roles of the microbiome in CRC carcinogenesis. Metagenomic and metabolomic data derived from faecal and/or tissue samples from patients with hereditary or suspected hereditary diseases and patients with serrated lesions may also be analysed to clarify other aspects of CRC tumorigenesis.

In conclusion, the present study highlights that dynamic shifts occur in microbial composition and metabolites changes during multistep CRC progression, suggesting their potential role in cancer progression, although it is not clear whether these species and metabolites directly cause tumorigenesis. Further investigations are needed to better define the role of microorganisms in CRC.

ORAL MUCOSA ORGANOIDS AS A WINDOW OF OPPORTUNITY FOR PERSONALISED CANCER THERAPY IN HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

HNSCC is an extremely heterogeneous disease, with a complex aetiology, involving cigarette smoking, alcohol consumption and human papilloma virus (HPV) infection.

Platinum-based chemoradiotherapy is still the cornerstone of treatment. Cetuximab, a monoclonal antibody blocking epidermal growth factor receptor, is an alternative with concurrent radiation for platinum-unfit locally advance patients or in combination with platinum-based doublets for recurrent/metastatic disease. Moreover, several studies have confirmed the role of immune checkpoint inhibitors in the advanced setting. Unfortunately, no other targeted drugs have been approved so far and no biomarkers have been identified to predict the effect of experimental treatments. However, according to The Cancer Genome Atlas,[5] 30% of HNSCC harbour a phosphatidylinositol 3-kinase (PI3KCA) alteration and clinical trials are exploring the value of inhibiting this pathway.

In this context, a paper recently published in *Cancer Discovery*[6] demonstrates the feasibility of the finest precision medicine approach, represented by the development of patient-derived organoids (PDOs). Some previous studies from the same group have demonstrated that PDOs faithfully recapitulate the original patient tumour characteristics and that they can be used to predict response to treatment, including also molecularly targeted agents. One of the main novelties is the development of oral mucosa organoids that can be used to model viral infections including the oncovirus HPV16, providing a tool to study this distinct subtype. Authors have developed a comprehensive biobank of HNSCCs-PDOs including all different primary sites and the matched normal mucosa organoids. One of the main strengths of this work is the characterisation of the potential spatial heterogeneity of this particular disease.

PDOs recapitulate the genomic and transcriptomic features of the original patient's tumour, both during culture and also on xenotransplantation. Maybe the most interesting part of this work, from a translational point of view, is the use of PDOs as a platform for drug screening. Although numbers are small, clinical response of patients treated with radiotherapy can be correlated to in vitro responses of the corresponding organoids. The co-treatment with LC161, a second mitochondria-derived activator of the caspase mimetic, overcomes radiotherapy resistance, giving an example of the use of organoids as a tool to explore novel radiosensitisers. Interestingly, the alpha-specific PI3K inhibitor alpelisib proved to be effective, independently of the specific PI3KCA mutation detected in the PDOs, whatever H1047R or E545K, for which differential sensitivities have been reported in the previous studies.[7] The fibroblast growth factor receptor (FGFR) inhibitor AZD4547 showed significant antitumour activity, despite the absence of *FGFR* molecular alterations, in a line harbouring a *KDR* mutation. In conclusion, this elegant paper highlights the potential of PDOs not only for drug screening but also in biomarkers discovery and it may represent a major advance in the development of precision medicine in HNSCC.

ACQUIRED HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) MUTATIONS IN OESTROGEN RECEPTOR (ER) POSITIVE METASTATIC BREAST CANCER CONFER RESISTANCE TO ER-DIRECTED THERAPIES

Targeting the ER with endocrine treatments is the preferred first-line therapy for advanced luminal breast cancer. However, almost all patients will eventually acquire endocrine resistance, with a proportion demonstrating primary resistance.[8] Beyond mutations in the ER gene (*ESR1*), which occur in 25%–30% of metastatic patients treated with aromatase inhibitors, identifying new mechanisms and novel target therapies with activity in resistant tumours is a key therapeutic challenge.

Nayar *et al* recently published in *Nature Genetics* an article that explores the role of HER2 mutations as a mechanism of resistance to oestrogen-directed therapies in ER positive metastatic breast cancer (MBC).[9] Using whole-exome sequencing, they analysed *ERBB2* mutations in metastatic tumours from a cohort of 168 patients with MBC. Nearly all patients were treated with prior endocrine therapy, including tamoxifen, aromatase inhibitors and fulvestrant. In 12 patients, they identified mutations in *ERBB2*, involving hotspot mutation in the kinase domain, as well as in the extracellular, transmembrane and cytoplasmatic domains. The study reported that 75% of HER2 alterations identified in the metastatic biopsies were not observed in primary tumour, indicating that they were acquired over the course of therapy. The authors provided evidence of HER2 alterations were clonally acquired, showing a clonal and subclonal evolution. And, they confirmed that *ESR1* and *ERBB2* mutations were mutually exclusive, consistent with other public data set.

To investigate the role of HER2 alterations as a mechanism of resistance to ER-directed therapy, they expressed with plasmids in the ER+ breast cancer cell lines T47D and MCF7 all HER2 mutant proteins observed in the 12 patients. Mutations in the kinase and transmembrane domain conferred resistant to oestrogen deprivation and anti-ER agents (tamoxifen, fulvestrant and GDC-0810). In contrast, wild-type HER2, as well as extracellular and cytoplasmatic domain mutations conferred intermediate resistance between *ESR1* and kinase and transmembrane domain mutants. Moreover, this work demonstrated transcriptional changes associated with HER2 mutations. *ESR1* and *PGR* were downregulated. This is indicative that ER signalling was suppressed in HER2 mutant cells. They also identified a HER2-MUT signature, which was enriched for *ERBB1* and *ERBB2* signalling, as well as RAS/MAPK signalling, and growth factor-driven ER signatures. Furthermore, two different mechanisms of activation of HER2 mutants were hypothesised: conformational changes to the catalytic domain of the receptor and constitutive HER2 homodimerisation.

This work finally studied the role of HER2 inhibition as a druggable target in ER+ cell lines. They showed that

low dose of neratinib resensitised HER2 mutant cells to fulvestrant and these cells were also sensitive to neratinib monotherapy at a higher dose. Interestingly, HER2 mutant cells were cross-resistant to palbociclib, both alone and in combination with fulvestrant. Neratinib, both as a single agent and with fulvestrant, led to repression of RAS/MAPK transcriptional activity and other transcriptional effects in HER2 mutant cells. These findings suggest that HER2 mutations are an acquired mechanisms of resistance to endocrine therapy for MBC that can be overcome by an irreversible HER2 inhibitor. This underlines the importance of serial profiling of metastatic disease at the time of progression in luminal MBC. Identification of HER2 alterations may help to identify patients to test new treatment strategies.

Contributors All authors contributed equally.

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