verified *in vitro*, and its targeting pathways were also investigated.

Results sEVs derived from radiated cells exhibited a stronger MDSCs induction capacity and MDSCs were more suppressive of T cell proliferation. MDSCs in ESCC bearing mice after radiation increased and the suppressive effect of MDSCs was improved. RNA-seq showed up-regulated PI3K-AKT pathway activity in MDSCs in ESCC bearing mice after radiation. sEVs from the plasma of ESCC-bearing mice after radiation-induced more MDSCs and had a stronger ability to induce immunosuppressive function of MDSCs. miRNA-26b in sEVs of ESCC cell lines and plasma of tumour-bearing mice were found to be up-regulated after radiation. miRNA-26b was found to have the ability to induce MDSCs expansion and function. miRNA-26b was found to activate PI3K-AKT pathway through targeting Pten.

Conclusions sEVs from ESCC cells after ionizing radiation had a stronger ability to induce MDSCs than sEVs 0gy in both promoting cell expansion and immunosuppressive function. *In vivo* study validated the MDSC-inducing function of radiation.

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THE ASSOCIATION BETWEEN EXERCISE, NUTRIENT AND FOOD HABITS WITH THE SINGAPOREAN GUT MICROBIAL COMPOSITION

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Background The impact of non-dietary lifestyle factors on the gut microbiota, such as physical activity, has not been frequently reported. Recent studies have suggested that exercise can increase the number of beneficial microbial species which enhance short-chain fatty acid synthesis and carbohydrate metabolism. Therefore, we investigated the relationship between physical activity and gut microbiome composition within a cohort of multi-ethnic healthy Singaporeans.

Methods 257 individuals completed the Global Physical Activity Questionnaire (GPAQ) (Armstrong et al. 2006) and Food Frequency Questionnaire (FFQ) (Whitton et al. 2017), to obtain quantitative measures of their physical activity, nutrition and dietary habits, respectively. They also provided paired stool samples, which underwent 16S rRNA V3-4 amplicon sequencing. Community and individual microbial features associated with physical activity were assessed using microbial ecology measures such as α -diversity and principal coordinate analysis (PCA), as well as, multivariate sparse Partial Least Squares analyses, whilst confounding for nutritional and dietary habits.

Results Using the GPAQ, 57% of the individuals were deemed to have an active lifestyle. Active individuals have increased microbial α -diversity, although not statistically significant. Unsupervised PCA analysis identified a subset of active individuals with distinct microbiome signatures, whereby these individuals, compared to those with sedentary lifestyles, have increased abundances of *Prevotella* spp., which is in keeping with their increased fibre intake. Sedentary lifestyle individuals were found to have increased abundance of *Lachnospirillum* spp., whereby phylogenetic similar microbial features (such as *Roseburia* and *Subdoligranulum* spp.) were significantly

Abstract IDDF2021-ABS-0169 Figure 1

correlated with more frequent eating out at hawker stalls and fast-food establishments (IDDF2021-ABS-0169 Figure 1. Correlation between gut microbiome with (a) nutrient intake; and (b) food habit). Studying the metabolic potential of the microbiome, active individuals had increased abundances of gene content related to energy production, whereby sedentary individuals had increased abundances of gene content related to degradation of aromatic compounds.

Conclusions Our study reaffirms that increased physical activity is associated with increased microbial diversity and beneficial microbial features. However, the differences in gut microbiota associated with physical activity may be due to differences in dietary intake and practices, rather than the exercise itself. Further studies investigating the link of gut microbiome and physical activity should control and standardize the dietary intake of participants.

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CANCER-ASSOCIATED FIBROBLASTS PROMOTE COLORECTAL CANCER PROGRESSION THROUGH IGF2-IGF1R-YAP1 AXIS

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Background Colorectal cancer (CRC) is one of the common cancers worldwide. The tumor microenvironment exerts crucial effects in driving CRC progression. Cancer-associated fibroblasts (CAFs) serve as one of the most important tumor microenvironment components. The study aims to elucidate the driving role of CAFs in CRC.

Methods Primary CAFs were isolated for RNA-seq analysis, and conditioned medium (CM) was collected from normal fibroblasts (NFs) and CAFs. CRC cells HCT116 and DLD1 were treated with NF-CM or CAF-CM respectively for functional tests. RNA-seq analysis of IGF2-stimulating HCT116 cells was performed to reveal the prominent downstream pathways. qRT-PCR, Western blot, immunofluorescence, and

immunohistochemistry were used to validate the gene expression. *In vivo* studies were performed by subcutaneous xenograft formation model to appraise the efficacies of small molecule co-administration.

Results CAFs-derived CM promoted proliferation, migration, and invasion of HCT116 and DLD1 cells (IDDF2021-ABS-0173 Figure 1A, IDDF2021-ABS-0173 Figure 1B, IDDF2021-ABS-0173 Figure 1C, IDDF2021-ABS-0173 Figure 1D, IDDF2021-ABS-0173 Figure 1E, IDDF2021-ABS-0173 Figure 1F, IDDF2021-ABS-0173 Figure 1G, IDDF2021-ABS-0173 Figure 1H, IDDF2021-ABS-0173 Figure 1I, IDDF2021-ABS-0173 Figure 1J). IGF2 was listed in the top high-expression genes in CAFs compared with NFs, and its predominant

Abstract IDDF2021-ABS-0173 Figure 1

Abstract IDDF2021-ABS-0173 Figure 2

Abstract IDDF2021-ABS-0173 Figure 3

Abstract IDDF2021-ABS-0173 Figure 4

receptor IGF1R serves as a prognostic marker to predict the unfavorable outcomes of CRC patients (IDDF2021-ABS-0173 Figure 2A, IDDF2021-ABS-0173 Figure 2B, IDDF2021-ABS-0173 Figure 2C, IDDF2021-ABS-0173 Figure 2D, IDDF2021-ABS-0173 Figure 2E, IDDF2021-ABS-0173 Figure 2F, IDDF2021-ABS-0173 Figure 2G, IDDF2021-ABS-0173 Figure 2H, IDDF2021-ABS-0173 Figure 2I, IDDF2021-ABS-0173 Figure 2J, IDDF2021-ABS-0173 Figure 2K). Apart from Akt-mTOR pathway, RNA-seq analysis revealed that YAP1 signaling serves as a prominent downstream modulator to mediate oncogenic signaling of IGF2-IGF1R. By single-cell RNA sequencing (scRNA-seq), IGF2 was found to be predominantly secreted by CAFs, while IGF1R-YAP1 was averagely distributed in CAFs and cancer cells. When stimulating IGF1R by rhIGF2, F-actin remodeling, nuclear accumulation of YAP1, and overexpression of YAP1 targets were observed, but these effects were attenuated by either IGF1R depletion or Picropodophyllin (IGF1R inhibitor) administration (IDDF2021-ABS-0173 Figure 3A, IDDF2021-ABS-0173 Figure 3B, IDDF2021-ABS-0173 Figure 3C, IDDF2021-ABS-0173 Figure 3D, IDDF2021-ABS-0173 Figure 3E, IDDF2021-ABS-0173 Figure 3F, IDDF2021-ABS-0173 Figure 3G, IDDF2021-ABS-0173 Figure 3H, IDDF2021-ABS-0173 Figure 3I, IDDF2021-ABS-0173 Figure 3J, IDDF2021-ABS-0173 Figure 3K, IDDF2021-ABS-0173 Figure 3L, IDDF2021-ABS-0173 Figure 3M, IDDF2021-ABS-0173 Figure 3N, IDDF2021-ABS-0173 Figure 3O). By in vivo studies, we found that co-targeting IGF1R and YAP1 by Picropodophyllin and Verteporfin (YAP1 inhibitor) achieved the anti-tumor effects in subcutaneous xenograft

and orthotopic implantation models. The synergistic effects were also validated in a patient-derived organoid with IGF1R-YAP1 co-upregulation (IDDF2021-ABS-0173 Figure 4A, IDDF2021-ABS-0173 Figure 4B, IDDF2021-ABS-0173 Figure 4C, IDDF2021-ABS-0173 Figure 4D, IDDF2021-ABS-0173 Figure 4E, IDDF2021-ABS-0173 Figure 4F, IDDF2021-ABS-0173 Figure 4G, IDDF2021-ABS-0173 Figure 4H, IDDF2021-ABS-0173 Figure 4I, IDDF2021-ABS-0173 Figure 4J). **Conclusions** This study revealed the promoting role of CAFs in CRC progression. The findings highlight the translational potential of IGF2-IGF1R-YAP1 axis, which may serve as a prognostic biomarker and therapeutic target for CRC.

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SARS-COV-2 ACTIVATES LUNG EPITHELIAL CELL PROINFLAMMATORY SIGNALING AND LEADS TO IMMUNE DYSREGULATION IN COVID-19 PATIENTS

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