Methods A comprehensive, computerized literature search from the electronic database of MEDLINE, Google Scholar, Cochrane Library and OVID was performed with the following search terms: colorectal cancer, coffee, and mortality. Three cohort studies were selected and validated using the Newcastle-Ottawa criteria. Multivariate results were combined under a random-effects model using pooled adjusted hazards ratio (HR). The Cochrane Review Manager Software version 5.4 was used for all analyses.

Results Three cohort studies comprising of 3723 patients were analyzed by pooling adjusted hazards ratio using the random-effects model. Coffee consumption was beneficial in reducing cancer-related mortality among CRC patients. Consumption of four or more cups of coffee per day resulted in a decrease in CRC-related mortality (RR 0.59, 95% CI 0.46-0.76, I² =0%) (IDDF2021-ABS-0178 Figure 1. Forest Plots - Four or More Cups of Coffee Per Day vs Non-Coffee Drinkers). Consumption of 2-3 cups per day was showed to also reduce cancer-related mortality among colorectal cancer patients (RR 0.77, 95% CI 0.66-0.91, I² = 0%) (IDDF2021-ABS-0178 Figure 2. Forest Plots – Two to Three Cups of Coffee Per Day vs Non-Coffee Drinkers).

Conclusions Coffee consumption is beneficial in reducing cancer-related mortality among diagnosed patients with CRC.

SLC25A22 DRIVES IMMUNE SUPPRESSION IN KRAS-MUTANT COLORECTAL CANCER

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Background Direct targeting of KRAS is challenging and represents an unmet need. We identified SLC25A22, a mitochondrial glutamate transporter, as a potential therapeutic target in KRAS mutant colorectal cancer (CRC). In this study, we reveal that SLC25A22 underlies mutant KRAS-induced immune suppression in CRC.

Methods Immune cell infiltration was determined by flow cytometry. The immunosuppressive effect and migration of MDSC were estimated by T cell suppression assay and trans-well assay, respectively.

Results Tumors from ApcMin/+KrasG12D Villin-Cre mice demonstrated marked infiltration in immunosuppressive myeloid-derived suppressor cells (MDSC) (P<0.001), but reduced T-cells (CD4+/CD8+) (P<0.05) (IDDF2021-ABS-0183 Figure 1. Kras-mutated tumors exhibit an immune-suppressive microenvironment). Tumor organoids derived from ApcMin/+KrasG12D Villin-Cre with or without SLC25A22 were injected into C57 mice. SLC25A22 knockout severely impaired tumor growth, with reduced MDSC (P<0.05) but increased CD4+/CD8+ T-cells (P<0.05, P<0.01). Consistent data were obtained from the syngeneic mouse models of murine CRC cell lines with Slc25a22 knockout. And there was a negative correlation between the percentage of MDSC and that of CD8+ T-cells in the xenograft tumour tissues (R²=0.592, P<0.001). Indeed, T cell proliferation was impaired after being co-cultured with MDSC in vitro. These results suggested that knockout of Slc25a22 reversed mutant KRAS-driven immune suppression, especially reduced the immunosuppressive MDSC infiltration (IDDF2021-ABS-0183 Figure 2. SLC25A22 knockout impaired tumor growth and reversed mutant KRAS-driven immune suppression in syngeneic mice, IDDF2021-ABS-0183 Figure 3. SLC25A22 knockout impaired tumor growth and reversed mutant KRAS-driven immune suppression in syngeneic mice).

Abstract IDDF2021-ABS-0183 Figure 1

Abstract IDDF2021-ABS-0178 Figure 1

Abstract IDDF2021-ABS-0178 Figure 2

Abstract IDDF2021-ABS-0183 Figure 1
Abstract IDDF2021-ABS-0183 Figure 2

Abstract IDDF2021-ABS-0183 Figure 3

Abstract IDDF2021-ABS-0183 Figure 4
Integrated RNA-sequencing and antibody array profiling identified C-X-C chemokines, in particular CXCL1/3, were depleted by SLC25A22 knockout. SLC25A22 loss reduced CXCL1/3 mRNA as well as secretion in CRC cells (IDDF2021-ABS-0183 Figure 4. SLC25A22 regulate the expression and secretion of chemokines CXCL1 and CXCL3). CXCL1/3 functions as chemoattractants for MDSC via its receptor CXCR2. Indeed, the conditioned medium from SLC25A22 knockout CRC cell showed impaired ability to promote MDSC migration compared to the control medium. CXCL1-siRNA, anti-Cxcl1 neutralizing antibody or CXCR2 inhibitor impaired SLC25A22-induced MDSC migration, inferring an underlying role of CXCL1-CXCR2 interaction and in attracting MDSC infiltration.

Conclusions Our work suggests a SLC25A22-chemokine axis that promotes an immune suppressive microenvironment in KRAS-mutant CRC and implies that SLC25A22 constitutes a novel target for immunotherapies.

**EXPLORING GUT MICROBIOTA COMPOSITION REGULATED BY PROBIOTICS AS A POTENTIAL THERAPEUTIC TARGET IN NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS**

Background Growing attention has been given to the effects of dysbiosis in the gastrointestinal tract that possibly modulate intestinal permeability. This will trigger the secretion of pro-inflammatory cytokines that induces inflammation. Thus, probiotics are suggested to reverse the mechanism by promoting the growth of good bacteria that participate in the modulation of intestinal epithelial defense responses. We aimed to evaluate the effects of probiotics on gut microbiota...