Supplemental Figure Legends

Figure S1. Global metagenomic characteristics of the fecal samples.

A. A heatmap showed overall microbiome composition grouped by phylum, including Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria and other phylum, in the 455 subjects, including 21 dMMR CRC, 207 pMMR CRC, and 227 CTRL.

B. A heatmap of differential species with relative abundances over $5 * 10^{-5}$ in the study cohort.

Figure S2. Global metabolomic characteristics of the fecal samples.

A heatmap of differential metabolites, categorized by superclasses, including lipids and lipid-like molecules, organic acids and derivatives, organoheterocyclic compounds, benzenoids, phenylpropanoids and polyketides, organic oxygen compounds, alkaloids and derivatives, nucleosides, nucleotides, and analogues, acetylides, and other metabolites, in the 418 subjects, including 14 dMMR CRC, 177 pMMR CRC, and 227 CTRL.

Figure S3. Differential gene expression and immune cell composition in dMMR CRC and pMMR CRC.

(A) A volcano plot shows the differential gene expression between 5 dMMR and 45 pMMR CRC. P values corrected by Bonferroni < 0.05 and log2 foldchange > 1.5 are considered significant.

(B) The box plot shows the immune cell composition in dMMR CRC and pMMR CRC. Data are delivered via the interquartile ranges (IQRs), with the median as a black horizontal line and the whiskers extending up to the most extreme points within 1.5× the IQR.

Figure S4. Microbial metabolic-host immune interactions in CRC.

(A) A heatmap of spearman correlation between MMR-associated metabolites and tumor-infiltrated immunocytes. $^*P < 0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

(B) A heatmap of spearman correlation between MMR-associated KO genes and tumor-infiltrated immunocytes. $^*P < 0.05$; $^{**}P<0.01$; $^{***}P<0.001$.