

Disentangling the roles of bacteria in colorectal cancer with a large-scale in vitro screening and genome scale metabolic models

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Abstract :

Members of the gut microbiome play critical roles in the start and progression of colorectal cancer (CRC). Some members produce toxins or display surface proteins that favor tumorigenesis, while others inhibit tumorigenesis, help maintain homeostasis, and outcompete potentially dangerous CRC-promoting strains. During tumorigenesis, the micro-environment of the tumor significantly changes and is accompanied by consistent changes in the composition of the surrounding microbiome. A detailed understanding of the role of the microbiome can be a key element to elucidate the external mechanisms that modulate CRC tumor formation. But it is currently challenging to tell apart the bacteria that mostly benefit from the tumor microenvironment from those that actively promote the development of tumors. It is also challenging to identify the exact bacterial mechanisms that influence tumorigenesis. To address these challenges, we tested the effect of the secreted products and surface proteins from over one hundred gut bacteria on the growth rates of CRC cells and associated this effect with both known virulence genes and novel microbial pathways. This large-scale in vitro analysis revealed how different bacterial families tend to inhibit or enhance cell growth, although these effects often depend on the presence of specific genes or pathways and thus may vary significantly even between closely related strains. We further developed a comprehensive statistical framework applied to the genome-scale metabolic models of over 1500 microbiome bacteria to assess which bacterial metabolism specifically depends or benefits from the tumor microenvironment. This framework allowed us to mechanistically explain why specific bacterial taxa are associated with CRC. This research has contributed to further our understanding of the effects of the gut microbiome on CRC development, and provide valuable resources towards the development of microbiome-based diagnostics and treatment strategies.

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