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Towards a cancer-chemopreventive diet

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Abstract

Commensal microbes engineered to convert natural compounds found in cruciferous vegetables into molecules with anticancer properties prevent carcinogenesis and cause the regression of colorectal cancer in mice fed with a vegetable diet.

Extensive epidemiologic and experimental work has unveiled an association between several foods and nutrients and the development of cancer^{1,2}. However, strategies based on dietary modification or nutrient supplementation have shown mixed success, which has limited their possibilities for clinical translation. The challenges are numerous. Chemopreventive metabolites derived from foods may be inaccessible due to inherently low bioavailability or to limitations in host absorption. Also, the optimal dose, duration, formulation and time window of exposure to dietary components that would maximally influence the development of neoplasia remain largely unknown. And the interpretation of studies based on cancer cell lines or on genetically engineered animal models is hindered by their limited ability to recapitulate the earliest stages of human carcinogenesis or the complexity of the mechanisms that underlie molecularly heterogeneous tumours.

Increased attention has therefore been dedicated to exploiting the interactions of diet and the gut microbiome — the population of microbes living in the human intestine. Gut dysbiosis (microbial imbalance or maladaptation) has been linked to cancer through either direct interaction with epithelial cells (this is the case of *Fusobacterium nucleatum* in colorectal cancer) or the host immune system (as with *Helicobacter pylori* in gastric cancer), or through indirect influences on local or distant tissues (for example, microbially mediated metabolism of sex steroids in oestrogen-driven breast, ovarian or endometrial malignancies)^{3–5}. Yet the understanding of how the microbiome can be leveraged to prevent or treat cancer is still in its infancy⁶. Because of its 100-fold greater genomic potential compared to the human genome, the gut microbiome functions as a metabolic organ, significantly contributing to the regulation of numerous host processes⁷, including the bioactivation of dietary metabolites central to diet-based chemoprevention strategies⁸. Therefore, engineering microbes to directly intervene in metabolic processes holds promise for the prevention or treatment of cancer. So far, microbes have been programmed to target pathogens, to restore dysfunctional host processes, to deliver drugs and to act as biosensors.

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Reporting in *Nature Biomedical Engineering*, Matthew Chang and colleagues now show that engineered commensal *Escherichia coli* can be used to enhance the efficacy of a chemopreventive dietary intervention to drive the conversion of diet-derived glucosinolates into bioactive sulphoraphanes, which possess anticancer activity⁹.

Dietary glucosinolates are hydrolysed into sulphoraphanes by myrosinase, a β -thioglucosidase enzyme that is found in the human microbiota. Chang and co-authors hypothesized that the delivery of an engineered commensal (*E. coli* Nissle 1917; *EcN*) could provide higher myrosinase catalytic activity during co-administration with a cruciferous vegetable diet high in glucosinolates. This combination could boost the in vivo bioavailability of sulphoraphanes to reach the requisite concentrations that would inhibit tumorigenesis. The authors screened several candidate β -thioglucosidase variants to identify myrosinases with the highest catalytic activity at the temperature and pH conditions expected within the human intestinal tract. Next, they demonstrated that the optimal myrosinase was able to facilitate conversion of sinigrin, a surrogate for dietary glucosinolate, and to inhibit growth in cancer cells. To localize *EcN* to tumour surfaces, the authors added a construct to facilitate surface overexpression of histone-like protein A (HlpA), which permitted microbial infiltration into tumour microenvironments through the binding of heparan sulfate proteoglycans, particularly syndecan 1, which are overexpressed on tumour cell surfaces. They then demonstrated that the optimized, engineered commensal microbe was functional in vitro, binding to cancer-cell surfaces with high affinity to catalyse sinigrin to acyl isothiocyanate (AITC), resulting in > 95% inhibition of the activity of colorectal cancer cells (but not breast or stomach cancer cells or smooth muscle cells).

On the basis of these in vitro data, the authors tested the in vivo efficacy of the engineered microbes in Balb/C mice treated with azoxymethane and dextran sodium sulfate, a chemical carcinogenesis model of colitis-associated colorectal cancer. Inoculation of mice with either engineered or control *EcN* by oral gavage and feeding with either a control diet or a diet supplemented with sinigrin or a cruciferous vegetable (broccoli) resulted in therapeutic outcomes. The mice fed with a supplemented diet showed reduced *EcN* colonization of colonic tissue and increased the concentrations of *EcN* in the faeces, which is consistent with the clearance of available tumour surfaces for *EcN* binding. Moreover, residual tumour surfaces appeared to overexpress heparan sulfate proteoglycans (compared to adjacent normal tissue), suggesting preferential HlpA-mediated *EcN* binding to tumour surfaces. After the intervention, histologic assessment showed a 75% reduction in tumours (with respect to controls), without signs of severe epithelial dysplasia or colorectal tract obstruction. Furthermore, colonic tissue incubated in vitro with the engineered *EcN* appeared to bind tumours and areas high in syndecan 1. And inoculation of the engineered *EcN* with HlpA binding affinity (adherent *EcN*) compared to *EcN* without HlpA binding (non-adherent *EcN*) yielded a two-fold increase in circulating plasma concentrations of downstream metabolites of sinigrin. Taken together, these findings strongly suggest that the administered engineered *EcN* localizes at tumour surfaces and facilitates the local conversion of glucosinolates to sulphoraphane, leading to the inhibition of tumorigenesis.

These promising results raise intriguing questions. How do additional host and host-extrinsic factors impact the efficacy of treatments with bioengineered microbes? Dietary metabolite

bioavailability — including colonization efficacy due to host factors, competition with other commensal microbes, variation in digestion and compliance to an intervention — would need to be optimized. Do these microbial interventions induce any toxicity? Notably, Chang and colleagues show that inoculation with engineered microbes is associated with significant bleeding. Although bleeding may have been more evident in the context of their colitis-associated tumour model, additional unforeseen adverse effects may accompany the introduction of engineered microbes; this would compromise the generally favourable benefit–risk balance of dietary interventions. Moreover, how critical is the direct binding of microbes to tumour surfaces to induce the chemopreventive effect? From a cancer-prevention standpoint, the ideal intervention would impact tumour initiation in pre-neoplastic tissue rather than in already established tumours. Moreover, a reliance on direct microbial interaction with tumour surfaces would limit dietary metabolite–microbe approaches to tumours that form within the gastrointestinal tract, and molecular heterogeneity within gastrointestinal tumours may further compromise approaches that depend on tumour binding. Also, does the effect of microbes on mucosal immunity play a role in the observed antitumour effect? It is possible that gut bacteria, even commensal species, trigger a host immune response or reactivate suppressed antitumour immunity, independently of any effects on microbial metabolism. In this regard, Chang and colleagues noted a possible increase in gut-associated lymphoid tissue following intervention.

Overall, Chang and co-authors provide compelling proof-of-concept evidence that commensal microbes may be leveraged as a modifiable vehicle to modulate host metabolism of diet-derived metabolites to elicit potent anticancer effects in the colon. Given the limited success of dietary interventions administered in isolation for cancer prevention^{10–13}, strategies for leveraging the gut microbiome as a safe and cost-effective complement to dietary chemoprevention should be further explored. Also, the authors' findings have broader implications for cancer prevention and interception. For example, commensal microbes could be engineered to augment the efficacy or reduce the toxicity of non-dietary chemopreventives, such as aspirin, for the prevention of colorectal cancer and other tumours (Fig. 1).

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Fig. 1 |. microbial engineering for the enhanced prevention and treatment of cancer.

Cancer-prevention strategies based on dietary modification or supplementation are typically limited by host characteristics that restrict the bioavailability of dietary metabolites. Similarly, the microbe-mediated conversion of dietary compounds into anticancer metabolites may be insufficient to reach the concentrations necessary to exert their effects. Engineered microbes can provide higher metabolic function in cases where native mechanisms are absent or limited in the human gastrointestinal tract. In cases where neoplastic lesions have already formed, engineered microbes may be able to specifically direct prevention strategies to tumour areas or to host antitumour defences within tumours. Engineered microbes may also be used as a cellular ‘chassis’ to perform a wide range of functions at tumour sites, including the eradication of oncogenic pathogens, the delivery or metabolization of antitumour drugs, the reactivation of immunity, and assisting in tumour detection.