REVIEW

Science-Driven Nutritional Interventions for the Prevention and Treatment of Cancer

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ABSTRACT In population studies, dietary patterns clearly influence the development, progression, and therapeutic response of cancers. Nonetheless, interventional dietary trials have had relatively little impact on the prevention and treatment of malignant disease. Standardization of nutritional interventions combined with high-level mode-of-action studies holds the promise of identifying specific entities and pathways endowed with antineoplastic properties. Here, we critically review the effects of caloric restriction and more specific interventions on macro- and micronutrients in preclinical models as well as in clinical studies. We place special emphasis on the prospect of using defined nutrition-relevant molecules to enhance the efficacy of established anticancer treatments.

Significance: The avoidance of intrinsically hypercaloric and toxic diets contributes to the prevention and cure of cancer. In addition, specific diet-induced molecules such as ketone bodies and micronutrients, including specific vitamins, have drug-like effects that are clearly demonstrable in preclinical models, mostly in the context of immunotherapies. Multiple trials are underway to determine the clinical utility of such molecules.

INTRODUCTION

The traditional idea that cancer is a cell-autonomous disease caused by (epi)genetically unstable cells has been replaced by a more "ecologic" view of malignant disease that is conditioned by the interaction of multiple different cell types within the tumor, embedded in systemic metabolic, inflammatory, or immune circuitries, and profoundly influenced by the local and distinct microbiota (refs. 1, 2; Box 1). In parallel, the idea has spread that cancer should not only be treated by agents targeting the neoplastic cells themselves but also with interventions in their ecosystem, leading to the design of antiangiogenic therapies and immunotherapies as well as to the consideration that protumorigenic processes such as inflammation and dysbiosis could be reversed to halt tumor progression (1, 3–5). Moreover, it has become increasingly clear that the success of antineoplastic therapies that were initially attributed to cell-autonomous effects, such as the cure of certain cancers by cytotoxic chemotherapies or the response of breast and prostate cancers to antiestrogens and antiandrogens, in fact, relies on organism-wide effects involving the microbiota and the immune system (6–9).

Obesity, now the worldwide most prevalent pathologic condition, has been recognized as (one of) the most important cancer-predisposing condition(s), progressively outcompeting tobacco as the leading cause (10, 11). Carnivorous mammals have a higher risk of developing cancer than noncarnivores (12), in apparent accord with the epidemiologic association between red meat consumption and neoplasia in humans (13). The positive association between alcohol consumption and cancer risk is well established, but less known is that coffee consumption is inversely associated with the risk of liver cancer (14). Hence, not only the quantity but also the quality of nutrients influences the likelihood of developing a malignant disease. Moreover, multiple studies have pinpointed specificities in the metabolism of cancer cells (oncometabolism) and the cancer-immune infiltrate (immunometabolism), as well as the possibility of therapeutically targeting such metabolic pathways (15), which strongly intersect with epigenetics (16). In this context, dietary interventions

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BOX 1: THE CANCER-RELEVANT ECOSYSTEM IN A NUTSHELL

Nutritional interventions do not only affect the metabolism of cancer cells themselves but also act on multiple additional elements including but not limited to:

- Stromal cells including cancer-associated fibroblasts, adipocytes, and vascular cells. Cancers may heavily rely on trophic or mechanical support by angiogenesis, local adipocytes, and myofibroblasts, which in turn are influenced by external factors including nutrient supply.
- Immunostimulatory and suppressive circuitries affecting cancer immunosurveillance. To thrive, cancer cells must escape immunosurveillance, a process that can be achieved by local or systemic immunosuppression. Fluctuations in nutrient supply affect immunometabolism and hence can weaken or restore immunosurveillance.
- Neuroendocrine factors. Variations in nutrient support affect the levels of circulating protein hormones [such as insulin, insulin-like growth factor-1 (IGF1), or leptin], steroids (such as glucocorticoids), and neurotransmitters (such as catecholamines), which all impact cancer by regulating trophic support or by modulating the cancer–immunity dialogue.
- Microbiota. The intestinal microbiota has a major impact on distant, nongastrointestinal cancers by determining the tonus of anticancer immune responses through their wide effects on general metabolism, immunoregulatory, and inflammatory circuitries, as well as on T- and B-cell repertoires.

Hence, the mechanistic comprehension of nutritional interventions requires an "ecological" view of the tumor microenvironment with its relationship to systemic metabolism, inflammatory, and immune effectors, as well as the gut microbiota. This implies that *in vitro* cultures of cell lines or patient-derived xenotransplants grown in severely immunodeficient mice provide a rather partial, if not entirely incorrect, reflection of tumor biology. Indeed, metabolic interventions that restrain the growth of cancer cells often also undermine the functionality of the immunosurveillance system, strongly advocating for experimentation in realistic settings.

are no more (dis)regarded as quackery but are increasingly given consideration in primary or secondary prevention, as well as possible adjunct therapies (17).

Intuitively, dietary effects of cancer appear plausible because long-term modifications in the quantity and quality of macronutrients and micronutrients have a major effect on body composition and organismal physiology. Unfortunately, as compared with pharmacology, the field of nutrition research is still in its infancy and afflicted by methodological flaws that limit the interpretation of observational and interventional studies, calling for a future shift from empirical to science-driven approaches (Box 2). Moreover, nutrition research heavily relies on epidemiologic association studies on large populations reporting small changes in risk that may be affected by multiple major confounding factors including socioeconomic status. A number of "healthy diets" avoid the toxicity of the "Western style" diet that includes excessive carbohydrates, red meat, salt, saturated fatty acids, trans-fatty acids generated during industrial food processing, and food additives (including emulsifiers), but lacks whole vegetables, fruit, and nuts, as well as fiber (18). Such comparatively "healthy diets" include the Mediterranean, vegetarian, and vegan diets, the so-called Paleolithic diet, the "diabetes risk reduction diet" (DRRD), the "dietary approach to stop hypertension" (DASH), as well as a variety of diets that respect the recommendations of the "healthy eating index" and its innumerous variations (19). All of them have a positive impact on the manifestation of neoplastic disease (19). Moreover, even after a cancer diagnosis, switching to such diets may reduce cancer-specific and overall mortality, for example in breast cancer patients under DRRD (20). However, we will refrain from discussing these diets in detail because they are not strictly defined by their composition and because their beneficial effects might rely more on the avoidance of noxious food items rather than on their intrinsic quality. Instead, we will focus on more rational, science-driven approaches concentrating on changes in the quantity of macro- and micronutrients.

Although clinical nutritionists mostly intervene in end-stage cancer patients to prevent or reverse sarcopenia and cachexia, often in the context of palliative care, here, we will center our attention on the effects of nutrition on the manifestation of cancer (in the context of prevention strategies) or as an auxiliary intervention that is combined with treatments administered with curative intent (such as surgery, chemotherapy, radiotherapy, targeted therapy, or immunotherapy). For the sake of the present discussion, we will classify nutritional interventions into fasting regimens, interventions on macronutrients, supplementation of micronutrients, and microbiota-centered interventions (Table 1). Moreover, whenever possible, we will examine the mode of action of such nutritional interventions on the procarcinogenic ecosystem. Indeed, there are prospects that molecular knowledge generated by nutritional studies will lead to the identification of specific compounds with drug-like anticancer effects.

FASTING REGIMENS

Undoubtedly, obesity is one of the major risk factors for developing and dying from cancer, and actually constitutes a poor prognosis factor for many malignancies (10, 11). One of the few exceptions to this rule, the "obesity paradox," concerns the improved immunotherapy responses of male patients compared with lean individuals with metastatic melanoma. The obesity paradox may be speculatively explained

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BOX 2: HOW TO CONVERT NUTRITION RESEARCH INTO A SCIENCE: FROM ALCHEMY TO CHEMISTRY

In preclinical pharmacologic experimentation, as well as in clinical assay evaluating drugs, chemically defined molecules are administered as single agents (or combinations of agents) in a highly defined regulatory space. This contrasts with nutritional studies, in which chemically undefined regimens that differ in their molecular composition not in one but rather in multiple constituents are compared for their effects on animals or patients in a much less rigorous framework. To improve the current standards of nutrition research, it would be necessary to:

- Unify nomenclature, for instance, on intermittent versus time-restricted fasting cycles, caloric restriction, Western versus Mediterranean diet, etc. Ideally, such a unified nomenclature should be backed up by official bodies such as the American Society for Clinical Nutrition and similar organizations.
- Standardize the composition of commercial chows for rodents or dietary formulations for patients with an obligation for the manufacturer to meticulously indicate their composition (by defining the ingredients and the industrial process or recipe leading to the final product) and to provide a chemical analysis with all raw data to attest the absence of major fluctuations in their composition.
- Introduce, whenever possible, the rigor of pharmacologic studies, meaning that experiments or clinical trials should ideally be designed to compare exactly the same nutritional conditions with the addition or suppression of one single chemically defined entity or molecule.
- Recommend not only that the raw data of experiments or trials should be conserved, but that, in addition, samples of the chows or diets, plasma, peripheral blood mononuclear cells, and fecal microbiota should be archived to allow their analyses with presently available methods, as well as their reanalyses with future, yet-to-be-developed technologies.
- Perform high-quality retrospective or prospective studies evaluating the potential impact of macronutrients and micronutrients contained in food items on human health. High quality implies that such studies are systemically accompanied by the objective assessment of the biochemical effects of such dietary components on patients (e.g., quantifying ketone bodies in low-carb diets, characterizing the circulating metabolome and lipidome in vegetarian and vegan regimens, or measuring vitamin concentrations in plasma or hair by mass spectrometry).
- Subject all retrospective and prospective studies to multivariate analyses to minimize bias inflicted by extraneous determinants including socioeconomic status, which often is the most impactful confounding variable in epidemiologic studies.

by the initial immunosuppression, hence lacking immunoselection of tumors developing in the context of obesity (21, 22). Moreover, in certain cancer types like lung cancer, head and neck cancer, and renal cell cancer, obesity postdiagnosis is associated with improved survival compared with lean individuals (11). Of note, certain cancer treatments (such as antiestrogens or androgen deprivation therapy) cause weight gain, which in turn predicts poor outcome in breast and prostate cancers (23). Logically, multiple studies have been designed to reduce caloric supply and/or to increase energy expenditure in cancer patients with the scope to improve body composition, fitness, quality of life, and therapeutic outcome. Unfortunately, the primary endpoints of most of these studies deal with body composition rather than with objective therapeutic responses (Table 2), meaning that there is ample room for the development of treatment-relevant dietary interventions. Here, we focus our discussion on nutritional interventions performed with the intention to improve patient prognosis as well as suitable mouse models.

Methods for Reducing Caloric Supply

Global caloric supply can be reduced by caloric restriction (CR) or a variety of intermittent fasting protocols. Chronic CR is the continuous reduction, day by day and meal by meal, of the global caloric intake without malnutrition. However, CR poses a logistic problem (requiring an accurate caloric count for each meal) with a consequent reduction in compliance, as well as a dose–response effect that has to be carefully calibrated to ensure sufficient CR without undernourishment (24). For this reason, other methods for reducing caloric intake have been proposed, in part spurred by the observation that CR is the most potent intervention known to protect against carcinogenesis, preserve health and function, and extend life span in laboratory animals. Indeed, these effects on health span and life span can be mimicked by temporary deprivation from food. Thus, mice kept on an intermittent or alternative day fasting regimen (meaning that one day of fasting is followed by one day of *ad libitum* feasting) exhibit a bidaily weight oscillation without any long-term weight loss, yet also exhibit an extension in longevity comparable with that obtained by CR (25). Although a direct comparison between fasting regimens between mice and humans is impossible (due to very different metabolic rates: a 24-hour fasting cycle causes mice to lose 10% of their weight), it appears that alternate-day fasting (24 hours of fasting followed by 24 hours of unrestrained food intake) improves cardiometabolic parameters in human volunteers as well (26). However, other regimens of periodic fasting (such as 2 days of fasting per week; ref. 27) have become fashionable as well. Time-restricted fasting (TRF) regimens in which rodents have access to food for several hours (e.g., 4 hours per day) protect against obesity, diabetes, and frailty (25), spurring similar dietary recommendations for humans. For example, it has been suggested to observe a 16-hour period (at least) each

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Table 1. Classification of nutritional interventions

Class	Subclass/example	Definition	Reference
Fasting regimens	Caloric restriction	Reduction in daily caloric intake without malnutrition	(24)
	Total	Total absence of caloric intake for one to several days	(24)
	Intermittent	Alternance of fasting day(s) with unrestricted feeding day(s)	(26, 27)
	Time-restricted feeding	Concentration of the everyday caloric intake within a short time window, intending to create a daily period of fasting (usually over 16 hours)	(28)
Global	Mediterranean	Eating pattern based on traditional Mediterranean food intake, with a predominant share of vegetables, fruit, nuts, whole grains, and plant- or fish-based unsaturated fat	(196)
	Vegetarian	Eating pattern based on plants and excludes meat. Variations can include or exclude different animal products (dairy products, eggs)	(197)
	Vegan	Eating pattern based exclusively on plant-based food	(197)
	Paleolithic	Evolutionarily justified diet, adapted from the food available in the Paleolithic age. It is mostly comprised of vegetables, nuts, whole grains, and seeds, with a reduced portion of meat	(198)
	DASH diet	Regimen defined in the "Dietary Approaches to Stop Hypertension" (DASH) clinical trial. It demonstrated a positive impact on hypertension and served as basis for further nutrition studies	(199)
Interventions on macronutrients	Low-carb	Reduction of carbohydrates consumption, typically under 25% of the global caloric intake	(200)
	Carb-free/ketogenic	Food plan strictly restricting carbohydrates, with increased fat and appropriate protein content. It is often defined by a fat:(protein + carbohydrates) ratio of 3:1 or 4:1	(81)
	Low-fat	Reduction of fat consumption, typically under 30% of the global caloric intake	(201)
Depletion of micronutrients	Methionine	Reduction of methionine, an amino acid critical for DNA and histone methylation as well as for the one-carbon metabolism, by lowering its dietary intake or by oral methioninase administration	(63, 64)
Supplementation of micronutrients	Vitamins	Organic compounds essential for health that cannot be synthesized (or not in sufficient amounts) by the organism, and thus must be provided by food	(94)
	Spermidine	One of the two natural polyamines, a class of small, positively charged molecules with polyvalent cellular functions and global antiaging effect. Spermidine can be synthesized by the organism and assimilated through food	(146)
	Oligo-elements	Mineral compounds essential for health in small quantities, and which excessive supply of can have detrimental effects	(94)
	Polyphenols	Organic compounds naturally present in plant-based food that contain at least one aromatic ring and one hydroxyl group	(151, 152)
	Omega-3 fatty acids	Polyunsaturated fatty acids with a double bound 3 carbons away from the terminal methyl group, distributed mostly among plant-based oils and fish-based food	(153)
Microbiota-centered interventions	Prebiotics	Compound that cannot be digested by human enzymes nor absorbed by the intestine, and that will serve as a substrate for the beneficial growth or activity of the intestinal microbiota	(3, 202)
	Probiotics	Orally-administered live microorganisms intended to colonize the intestinal microbiota	(3, 202)
	Synbiotics	Oral formulation containing complementary pre- and probiotics	(3, 202)
	Postbiotics	Metabolic products released by the microbiota that have direct or indirect beneficial effects on their host	(3, 202)

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Table 2. Dietary interventions on macronutrients

Class	Subclass	Protocol	Cancer type	Therapeutic intervention	Phase	Status	NCT
Fasting regimen	*Calorie-restricted diet*	15%-decreased caloric intake with reduced fat and glycemic content + exercise	B-cell acute lymphoblastic leukemia	Chemotherapy	Phase II	Recruiting	NCT05082519
		25%-decreased caloric intake for 3–12 weeks prior to definitive cancer surgery	Breast/endometrium/prostate cancer	Surgery	n/a	Active, not recruiting	NCT02983279
		25%-decreased caloric intake 1 week before and 5–11 weeks after radiotherapy	Breast cancer	Radiotherapy	Phase II	Recruiting	NCT04959474
		50%-decreased caloric intake 2–3 days before chemotherapy + exercise	Breast cancer	Chemotherapy	Phase II	Enrolling by invitation	NCT03795493
		5 days every 3 weeks calorie-restricted diet (fasting-mimicking diet: 700 kcal on day 1, 300 kcal on days 2–4 and 450 kcal on day 5 ± metformin 1500 mg/day)	Lung adenocarcinoma	Chemoimmunotherapy	Phase II	Recruiting	NCT03709147
		5 days every 3 weeks calorie-restricted diet (fasting-mimicking diet: 600 kcal on day 1 then 300 kcal on days 2–5 ± metformin 1700 mg/day)	Breast cancer	Chemotherapy	Phase II	Recruiting	NCT04248998
		Very low calorie (350–400 kcal vegetable juice) 24–60 hours before and 24 hours after chemotherapy	Breast/ovarian cancer	Chemotherapy	n/a	Recruiting	NCT03162289
		Low-calorie diet 72 hours before, during, and 24 hours after chemotherapy (not detailed)	Breast/prostate cancer	Chemotherapy	Phase II	Recruiting	NCT01802346
		Two-year caloric restriction (not detailed)	Breast cancer	Preventive	Phase III	Active, not recruiting	NCT02750826
	Short-term fasting	24-hour fasting before and 24 hours after surgery	Colon cancer	Surgery	n/a	Active, not recruiting	NCT04345978
		48-hour fasting before and 24 hours after immunotherapy	Skin neoplasms	Immunotherapy	Phase I	Recruiting	NCT04387084
		Overnight fasting and 4 hours after chemotherapy	n/a	Chemotherapy	Phase I	Recruiting	NCT03892018
		96-hour fasting after surgery	Esophageal cancer	Surgery	n/a	Recruiting	NCT03676478
		24 hours fasting before and 24 hours after chemotherapy	Colorectal carcinoma	Chemotherapy	n/a	Enrolling by invitation	NCT04247464
	Short-term fasting + time-restricted KD	5-day fasting during chemotherapy and 23/1-hour fasting/eating KD between cycles	Glioblastoma	Chemoradiotherapy	n/a	Recruiting	NCT04730869
	Time-restricted eating	16/8 hour fasting/eating cycles for 3 months	Chronic lymphocytic leukemia	None	Phase I	Active, not recruiting	NCT04626843

(*continued*)

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Table 2. Dietary interventions on macronutrients (*Continued*)

Class	Subclass	Protocol	Cancer type	Therapeutic intervention	Phase	Status	NCT
Intervention on macronutrients	*Low-carbohydrate diet*	Low-carbohydrate diet ± high-dose vitamin C for 12 weeks	Colon cancer	Chemotherapy/ Targeted therapy	n/a	Not yet recruiting	NCT04035096
		Low glycemic index food + high-dose vitamin D for 33 months after surgery	Breast cancer	n/a	Phase III	Active, not recruiting	NCT02786875
		Low-carbohydrate diet (<20 g carb/day) for 6 months	Prostate cancer	Preventive	Phase II	Recruiting	NCT03679260
	Calorie-restricted KD	Calorie-restricted KD (<25 kcal/kg/day) from resection until 6 weeks after chemoradiotherapy treatment	Glioblastoma	Chemoradiotherapy	n/a	Active, not recruiting	NCT01535911
		Calorie-restricted continuous 4:1 KD (< 1,600 kcal/day), continuous starting from radiotherapy	Glioblastoma	Chemoradiotherapy	Phase II	Active, not recruiting	NCT02302235
	Isocaloric KD	Continuous 3:1 KD	Pediatric brain tumors	Chemotherapy	n/a	Recruiting	NCT03591861
		Continuous KD from treatment onset (± metformin 1,700–2,550 mg/day)	Glioblastoma	Targeted therapy	Phase II	Not yet recruiting	NCT05183204
		Continuous 2:1 KD for one year	Renal cell carcinoma	Targeted/Immunotherapy	n/a	Recruiting	NCT04316520
		Continuous KD for 16 weeks	Glioblastoma	Chemoradiotherapy	Phase I	Active, not recruiting	NCT03451799
		Continuous KD for 12 weeks	Mantle cell lymphoma	None	n/a	Recruiting	NCT04231734
		Continuous 3:1 KD during chemotherapy (12 weeks)	Breast cancer	Chemotherapy	n/a	Not yet recruiting	NCT05234502
		Continuous KD (<40 g carbs/day), discontinuous KD (15 days on-15 days off), or 3-hydroxybutyrate oral supplement (>1 g/kg/day) for 12 weeks	Renal cell carcinoma	Immunotherapy	n/a	Not yet recruiting	NCT05119010
		Continuous modified KD (Atkins diet, <20 g carbohydrates/day)	Glioblastoma	n/a	n/a	Active, not recruiting	NCT03278249
		Continuous KD (<30 g carb/day, 1.5 g proteins/day) during chemotherapy	Pancreatic cancer	Chemotherapy	Phase II	Recruiting	NCT04631445
		Continuous KD 7 days before and during treatment cycles	Follicular lymphoma/ Endometrial cancer	Targeted therapy	Phase II	Recruiting	NCT04750941

Abbreviation: KD, ketogenic diet.

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day without any caloric intake (28). However, in a phase III clinical trial, the combination of TRF and CR was not more efficient in improving metabolic health than CR alone (29). Prolonged fasting, often in the form of a drastic reduction of caloric intake per day (e.g., 200 to 400 kcal) for several days in a row and even several weeks is practiced by some, mostly overweight persons, often in specialized clinics that provide relaxation and distraction with mild exercise (30). Recently, so-called fasting-mimicking diets (FMD) have been developed in the form of plant-based food bars (34%–54% of normal caloric intake; 11%–14% proteins, 42%–43% mostly complex carbohydrates, 44%–46% fats) that are given as a substitute to any other caloric intake, usually for several subsequent days (e.g., 4–7 days) followed by an FMD-free interval (16–23 days; ref. 31) to treat a panoply of different conditions including obesity and metabolic syndrome (32). Subjects undergoing FMD cycles manifest an 11% reduction in blood glucose, a 24% reduction in circulating insulin growth factor-1 (IGF1), a 1.5-fold increase in IGF1 binding protein-1 (IGFBP1), and a 3.7-fold increase in serum ketone bodies (31).

Caloric restriction mimetics (CRM) are pharmacologically active molecules that cause some of the favorable biochemical and metabolic changes induced by CRs, though without a reduction of caloric supply (33). Many CRMs reduce the lysine acetylation of cytoplasmic proteins, a phenomenon that has also been observed upon fasting, thereby stimulating the process of autophagy (34, 35). Autophagy is a core mechanism of cellular and organismal homeostasis that critically contributes to the cell-autonomous suppression of oncogenesis and also improves anticancer immune surveillance in mice (36, 37). However, other mechanisms such as an increase in endogenous H_2S production stimulating evolutionarily conserved nutrient sensing and stress response pathways have been proposed to account for the beneficial health effects of fasting as well (38).

Tumor-Preventive and Anticancer Effects of Fasting Regimens

In many preclinical models, different strategies of dietary restriction have potent tumor-preventive or cancer therapy–amplifying effects. In mice, deletion of the genes coding for FOXO1 (which stimulates autophagy) and NRF2 (which activates antioxidative and carcinogen-detoxifying enzymes) abolishes suppression of carcinogenesis by CR while preserving life span extension (39, 40). CR reduces cancers in *TP53*-deficient mice (41), as well as in aging rhesus monkeys (42, 43). Prolonged nightly fasting is associated with a reduced incidence and recurrence of human breast cancer (44). Moreover, in mice, combinations of targeted therapy or chemotherapy with fasting regimens yield superior tumor growth control, a phenomenon that has been observed in human cancers transplanted into immunodeficient mice (45, 46), yet appears to be particularly potent in the context of an intact immune system (47). Thus, the abundance of dendritic cells (DC) and the ratio of cytotoxic T lymphocytes (CTL) over regulatory T cells (Treg) in the tumor infiltrate are favored by fasting regimens (48). Moreover, in mice, a 2-day fasting period enables the eradication of established cancers by a combination of chemotherapy and PD-1 blockade (49).

Mechanistically, nutrient deprivation inhibits intracellular nutrient sensors (such as the protein kinase mechanistic target of rapamycin complex 1, mTORC1, and the acetyltransferase EP300), activates sensors that sense nutrient scarcity (such as AMP-activated kinase, AMPK, and the deacetylases SIRT1 and SIRT3), and enforces catabolic reactions (glycogenolysis, proteolysis for gluconeogenesis and lipolysis coupled to ketogenesis) with consequent stimulation of adaptive cellular stress responses (including autophagy, antioxidant defense, and DNA repair; ref. 24). In cancer cells, fasting-induced autophagy facilitates the release of ATP, in particular in the context of chemotherapy, resulting in the recruitment of DCs into the tumor bed via an action on purinergic receptors, hence setting off anticancer immune responses (48). FMD also sensitizes mouse cancer to lysis by CTLs via the downregulation of the cytoprotective enzyme heme-oxygenase-1 (HO-1; ref. 47). At the systemic level, fasting causes a decrease of potential tumor cell trophic factors including glucose, insulin, IGF1, and leptin, as well as a reduction of inflammatory markers [including C-reactive protein (CRP) and circulating cytokines such as IL1β and IL6] and proarteriosclerotic low- and very-low-density lipoprotein, LDL and VLDL), all of which have procarcinogenic features. Fasting entails an increase in free fatty acids and anti-arteriosclerotic high-density lipoprotein and metabolically relevant hormones (such as ghrelin, adiponectin, and FGF21; ref. 24). Healthy diet and exercise, especially in combination, reduce endogenous estrogens in women (11), an effect that may explain the beneficial effect of leanness on the risk of postmenopausal breast cancer (50). Altogether, these findings suggest that dietary restriction mediates anticancer effects through multiple parallel signaling pathways (Fig. 1).

Immune Effects of Fasting

Several among these fasting-induced downstream signals have potential anticancer effects, in part through an action on the immune system. For example, in mice, administration of the ketone body 3-hydroxybutyrate is sufficient to boost the immune control of cancer in the context of PD-1 blockade (51). Furthermore, pharmacologic inhibition of mTORC1 enhances vaccination responses in clinical trials (52), and the inhibition of EP300 or the activation of SIRT1 improves the therapeutic efficacy of chemotherapy in preclinical models, in part through the activation of autophagy in tumor cells (48). Similarly, pharmacologic inhibition of IGF1 or IGF1 receptor (IGF1R) signaling induces autophagy in cancer cells and can be advantageously combined with chemotherapy and immunotherapy in mice (53, 54), corresponding to the observation that systemic administration of recombinant IGF1 protein annihilates the antitumor activity of CRMs in mice (48). In patients with non–small cell lung cancer (NSCLC), high circulating levels of IGF1 or high local IGF1R expression correlates with resistance to immunotherapy targeting PD-1/PD-L1 (54), indicating that the IGF1/IGF1R pathway might constitute a target for therapeutic interventions. Of note, in patients with mammary carcinoma, FMD increases the T-cell infiltrate (55), suggesting improved cancer immunosurveillance (48), which is of cardinal importance for the outcome of breast cancer treated with neoadjuvant chemotherapy (56). Accordingly, FMD augments the probability of radiologic and pathologic responses in such patients (57). FMD effects on cancer outcome are currently being investigated in two trials

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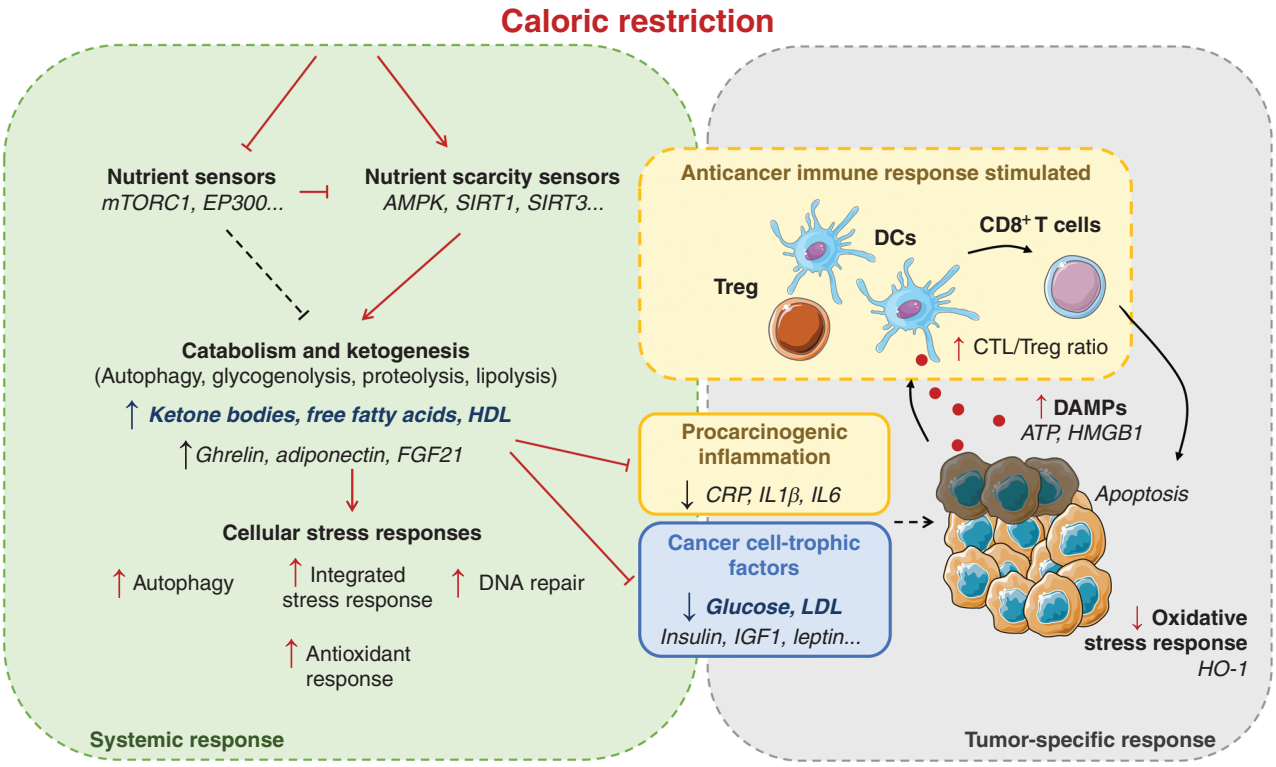

Figure 1. Anticancer effects of reduced caloric intake. A decrease in caloric intake activates nutrient scarcity signaling pathways and triggers a global metabolic shift—toward catabolism and ketogenesis—as well as an integrated cellular stress response. Cell adaptations to the nutrient restriction-induced stress include autophagy, DNA repair, and antioxidant response at the systemic level. In consequence, circulatory procarcinogenic factors are downregulated: those include inflammatory factors such as IL1β, IL6, and CRP, but also metabolic regulators such as glucose, insulin, insulin growth factor-1 (IGF1), and leptin, which nurture the tumor microenvironment. Finally, calorie-restricted tumors are sensitized to oxidative stress, and autophagy induction favors ATP release, which in turn attracts activate dendritic cells (DCs) into the tumor bed, ultimately stimulating anticancer immune responses by $CD8^+$ T cells. AMPK, AMP-activated protein kinase; EP300, E1A binding protein P300; FA, fatty acids; FGF21, fibroblast growth factor 21; HDL, high-density lipoprotein; HO-1, heme-oxygenase 1; LDL, low-density lipoprotein; mTORC1, mammalian target of rapamycin complex 1; SIRT1, sirtuin 1; SIRT3: sirtuin 3.

dealing with locally advanced breast cancer under chemotherapy (NCT04248998) and lung adenocarcinoma under chemoimmunotherapy (NCT03709147; Table 2).

In sum, it appears that different fasting regimens improve the therapeutic response to cancer treatments through a variety of different mechanisms that may favor immunosurveillance (Fig. 1). Multiple clinical trials are evaluating the capacity of such fasting regimens to improve the efficacy of standard-of-care treatment of a variety of different cancers (Table 2). Obviously, such trials exclude patients who are on the way to developing cachexia or sarcopenia for which fasting regimens might be harmful. In preclinical models, some of the beneficial effects of fasting can be mimicked by small molecules that induce autophagy (CRMs), elevate ketosis (3-hydroxybutyrate), or inhibit trophic kinases (IGF1R or mTORC1), suggesting the possibility of replacing fasting by controlled pharmacological interventions.

INTERVENTIONS ON MACRONUTRIENTS

The three categories of macronutrients (carbohydrates, lipids, and proteins) are not equivalent among each other because they cannot be interconverted by the human organism. Thus, lipids cannot be used to generate carbohydrates (but carbohydrates can be converted into lipids), and neither lipids nor carbohydrates can be used to generate essential amino acids required for protein synthesis (58). For this reason, shifts in the distribution among the three categories have a major impact on metabolism and body composition, as well as on cancer progression (Fig. 2).

Figure 2. Anticancer effects of macronutrient-depleting regimens. Protein reduction induces endoplasmic reticulum (ER) stress in cancer cells, thus stimulating the release of C-X-C motif chemokine ligand 10 (CXCL10) and IFNγ. Protein reduction also weakens immunosuppression by tumor-associated macrophages (TAM). The absence of exogenous methionine supply in plant-based diets affects one-carbon metabolism and decreases DNA and histone methylation. The methionine salvage pathway produces polyamines that trigger autophagy. Carbohydrate restriction prevents the noxious effects of addictive sugars, prevents nonalcoholic steatohepatitis (NASH), stabilizes the intestinal barrier, and reduces local and systemic inflammation. At the level of malignant cells, low-carb diet reduces trophic support and sensitizes to oxidative stress. A ketogenic diet cuts off the glucose supply of cancer cells, which, however, can adapt to their metabolism. Ketone bodies such as 3-hydroxybutyrate downregulate immunosuppressive signaling such as C-X-C motif chemokine ligand 12 (CXCL12) secretion and expression of programmed death-ligand 1 (PD-L1) on tumor antigen-presenting cells (APC), enhancing T cell–mediated immunity. DCs, dendritic cells; HMG-CoA, β-Hydroxy β-methylglutaryl-coenzyme A; HO-1, heme-oxygenase 1; OXCT-1, 3-oxoacid CoA-transferase 1; SAH, S-adenosyl-homocysteine; SAM, S-adenosyl-methionine.

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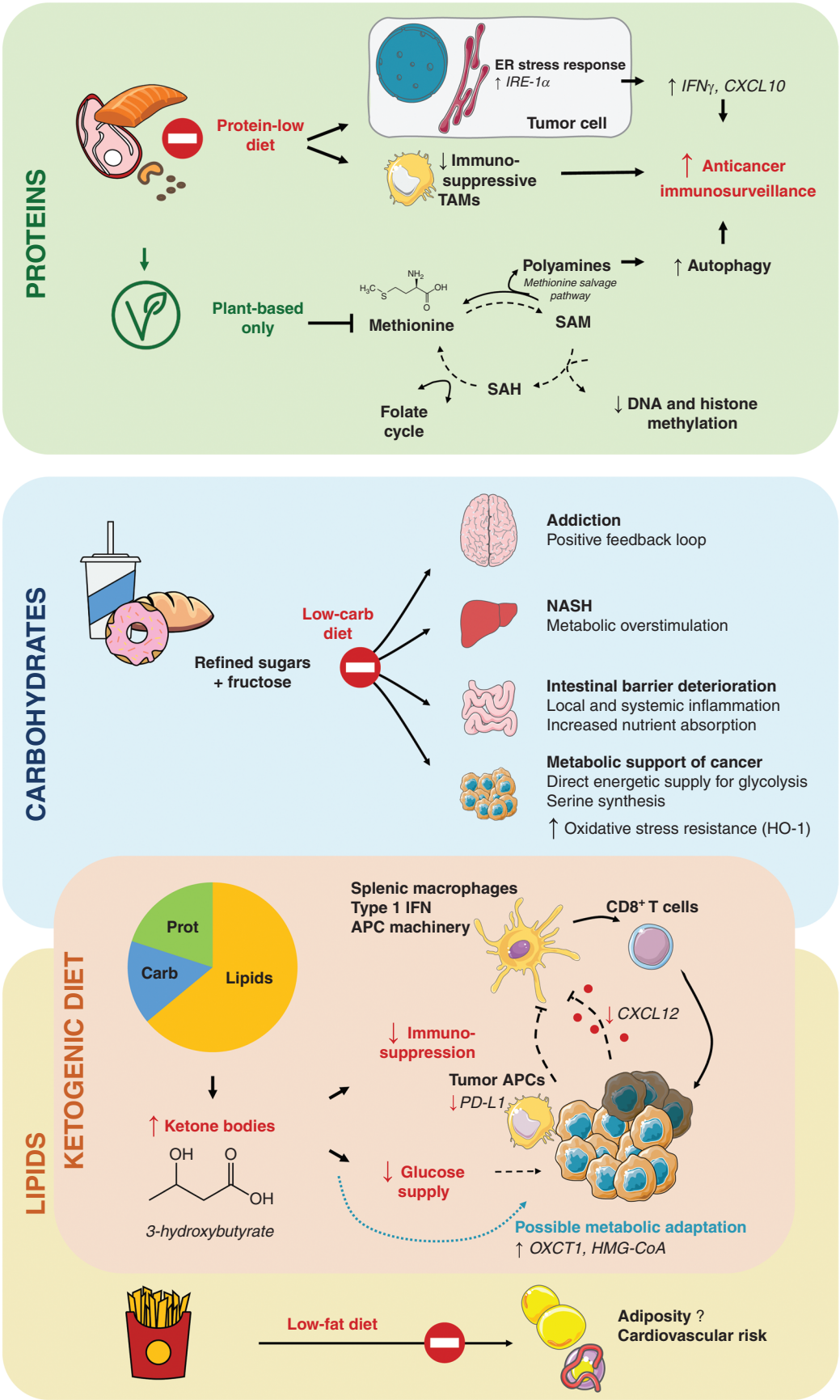

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Low-protein diets have been rarely applied to cancer patients, although the available evidence suggests that such diets reduce tumor growth in mice, an effect that is mediated by the induction of the IRE-1α arm of the endoplasmic reticulum (ER) stress response with the subsequent production of immunostimulatory cytokines (such as IFNγ and CXCL10) by cancer cells, hence improving immunosurveillance (59). This effect has been found when dietary protein was lowered to 14.9% of total calories (59). A low-protein diet also reportedly delays the surge of circulating tumor cells in a mouse model of breast cancer (60) and attenuates tumor infiltration by immunosuppressive tumor-associated macrophages in mouse models of renal and prostate carcinoma (61). Epidemiologic studies have associated cancer risk with the ingestion of animal (as opposed to plant) protein (62). However, given that such shifts affect multiple food ingredients (including the absorption of complex carbohydrates, dietary fibers, and polyphenols with plant-derived food items), it is impossible to conclude whether a reduction in the consumption of essential amino acids may account for such effects.

Plant-based vegan diets (which exclude any animal products) tend to be low in protein and in particular in methionine, perhaps providing a biochemical basis for their alleged health-promoting effects (63). Alternatively, methionine can be depleted by the oral administration of methioninase (64). The dietary restriction of methionine increases the longevity of mice, likely through the enhanced generation of cholic acid and the induction of autophagy (65). Methionine is the precursor of the universal methyl donor S-adenosyl-methionine (SAM). Hence, methionine depletion has a major effect on SAM and DNA and histone methylation in mice (16). Upon donation of its methyl group, SAM yields S-adenosyl-homocysteine (SAH). SAH can be hydrolyzed to homocysteine, which then either can be trans-sulfurated to cysteine or receive a methyl donation from the folate cycle to regenerate methionine. Hence, this cycle is closely intertwined with the folate cycle (fueled by serine and glycine), collectively forming the two major components of one-carbon metabolism. This metabolic pathway functions to incorporate nutritional carbon units into a variety of critical cellular processes (including purine and pyrimidine synthesis as well as methylation of DNA and protein). Of note, methionine can be recycled from SAM-dependent polyamine biosynthesis via the product methylthioadenosine (MTA), which fuels the methionine salvage pathway (66). Methionine restriction hence can increase the production of polyamines such as spermidine, which induces autophagy (67). Methionine restriction of mice reduces the growth of patient-derived xenografts and autochthonous sarcomas (68). In a clinical trial, oral administration of methioninase to patients with metastatic prostate cancer led to a reduction in PSA levels (69). However, it remains to be seen whether the benefits of methioninase extend to the clinical level and yield an increase in progression-free and overall survival.

Avoidance of Carbohydrates

Traditionally, it has been thought that high-fat diets are intrinsically obesogenic (which is true for mice, which normally live on carbohydrate-rich grains) and lipotoxic, spurring dietary recommendations and marketing campaigns in favor of low-fat diets. This contention has now been superseded by the idea that high-sugar diets, in particular refined sugars, are not only addictive (70) but also toxic for the human organism (58). As a result of the massive use of high fructose corn syrup (HFCS) and refined sugar (sucrose, a disaccharide composed of glucose and fructose), the consumption of fructose has been multiplied in the Western world (and in particular in the USA) by more than 100-fold, contributing to the pathogenesis of NASH through complex direct metabolic effects on the liver as well as through intestinal barrier deterioration, leading to bacterial liposaccharide-induced inflammation (71). Indeed, fructose mediates toxic effects on the gut leading to epithelial barrier deterioration (72), and its intestinal metabolites (such as glycerate; ref. 73) may account for part of its toxicity in mice. In addition, fructose may enhance the capacity of the intestine to absorb nutrients, hence contributing to adiposity (74), which arguably is the most important risk factor for multiple cancers. Dietary fructose increases the growth of prostate cancers *in vitro* and *in vivo*, in mouse models, and fructose levels in the serum of patients with prostate cancer are significantly higher than in healthy subjects (75). In patients with acute myeloid leukemia (AML), fructose levels are elevated in the bone marrow (76), and fructose feeds into the serine synthesis pathway to facilitate leukemia progression (77). In mice with the APC^{min} mutation, the development of intestinal tumors is accelerated by HFCS, likely through direct metabolic effects of fructose on (pre-)malignant cells (78). High levels of dietary fructose upregulate cytoprotective enzyme heme-oxygenase-1 (HO-1) in melanoma, thereby increasing resistance of the tumors to immunotherapy (79). Several clinical trials evaluate the effects of low-carb diets on cancer patients (Table 2). Given the high toxicity of fructose, it should be recommended at the population level to minimize the consumption of HFCS and refined sugars (72, 80). In contrast, the consumption of another type of carbohydrates should be recommended. Indeed, dietary fibers, which are mostly composed of complex, nondigestible carbohydrates, are associated with a reduced overall cancer risk, likely due to their effects on the intestinal microbiota (see below).

Ketogenic diets are low-carbohydrate, high-fat, and adequate protein diets, the adhesion to which is logistically complicated and that are typically affected by a similarly low compliance as for any other major dietary intervention (58). In response to this diet and the consequent rapid decline in circulating glucose levels, the bioenergetic metabolism is rewired to generate ketone bodies from fatty acids and ketogenic amino acids. Ketone bodies, in particular 3-hydroxybutyrate (and less so acetoacetate), which are produced from acetyl-coenzyme A in the liver, can reach millimolar concentrations in the plasma and replace glucose as an essential fuel, for instance, for the maintenance of brain function (81, 82). It has long been argued that cancer cells are particularly glucose-dependent (the Warburg effect) and that carbohydrate starvation, hence, would be a specific way to treat malignant disease. Indeed, in rodent models, the ketogenic diet synergizes with phosphoinositide-3-kinase inhibitors to restrain tumor growth (83). However, the glucose dependence of cancer is not a general phenomenon. Thus, in mice, hepatocellular carcinoma can acquire the capacity (that normal

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hepatocytes lack) to consume ketone bodies by upregulation of 3-oxoacid CoA-transferase 1 (OXCT1; ref. 84). Some cancers, such as pancreatic ductal adenocarcinoma (PDAC), upregulate HMG-CoA lyase to produce 3-hydroxybutyrate as a fuel for tumor progression, and intraperitoneal injection of 3-hydroxybutyrate promotes liver metastasis of PDAC in mice (85). Preclinical experimentation has shown that a ketogenic diet improves cancer immunosurveillance by downregulating the expression of ligands of inhibitory receptors PD-1 and CTLA-4 [such as PD-L1 and CD86 in splenic myeloid cells (48) or tumor cells (83)], by augmenting the expression of type 1 IFN and antigen presenting–relevant gene (83) as well as by increasing infiltration of tumors by Th1 cytokine producing $CXCR3^+$ $CD8^+$ T cells (86). Moreover, the ketogenic diet sensitizes to immunotherapy with antibodies targeting PD-1 or CTLA-4 (51, 86). Mechanistically, the ketogenic diet activates AMPK, which phosphorylates PD-L1 on Ser283, triggering the degradation of the inhibitory PD-1 ligand. Moreover, AMPK phosphorylates EZH2, culminating in increased type 1 IFN and antigen presentation (83).

Importantly, the ketogenic diet may be replaced by oral administration of 3-hydroxybutyrate. Indeed, in mice, 3-hydroxybutyrate improves cancer immunosurveillance through an effect on GTP protein-coupled receptor 109A (GPR109A) and prevents the upregulation of PD-L1 on myeloid cells, which is usually observed in the context of PD-1 blockade (51). In addition, 3-hydroxybutyrate has a direct inhibitory effect on the NLRP3 inflammasome, suggesting that it has additional immunomodulatory effects (87). However, it remains to be seen whether all beneficial effects of a ketogenic diet can be mimicked by 3-hydroxybutyrate, which is currently tested in a phase II study in advanced first-line kidney cancer patients (NCT05119010; Table 2). Moreover, it appears that, in specific cases, as discussed above, 3-hydroxybutyrate can fuel tumor growth and stimulate metastasis, as exemplified for murine hepatocellular carcinoma (84) and PDAC (85).

Ketogenic diets have been evaluated in clinical trials to show reduced total and android fat mass, as well as circulating IGF-1 levels, in women with ovarian or endometrial cancer, though without any reported effects on malignant disease (88). Randomized trials reported reduced body fat and tumor size, as well as improved overall survival in women with locally advanced or metastatic breast cancer treated with neoadjuvant chemotherapy in the context of a 3-month-long ketogenic diet (89, 90). This effect was coupled to reduced circulating tumor necrosis factor-α (TNFα) and insulin levels (89). The ketogenic diet also improved biomarkers of metabolic health (creatinine, IGF1, free triiodothyronine, gamma-glutamyl-transpeptidase, triglycerides) and subjective well-being in women with breast cancer undergoing radiotherapy, though without effects on the clinical response (91), and similar metabolic and subjective effects have been reported for patients with rectal cancer under radio-chemotherapy (92), coupled to a trend toward improved pathologic tumor responses (93). Additional trials are now under way to evaluate the potential beneficial effects of a ketogenic diet on cancer progression (Table 2).

In conclusion, there is limited evidence that isocaloric shifts among macronutrients have anticancer effects, a hypothesis that nonetheless is being evaluated in multiple clinical trials. However, there are some hints that ketogenic diets are beneficial in the context of cancer treatments. It will be particularly interesting to compare the clinical efficacy of the ketogenic diet with direct administration of the ketone body 3-hydroxybutyrate.

INTERVENTIONS ON MICRONUTRIENTS

Rewiring of cancer cell metabolism constitutes one of the hallmarks of neoplastic disease (1). In spite of historical assumptions that cancer cells would uniformly switch metabolism to higher glucose dependency (94), it has become clear that each oncogenic pathway is linked to different alterations of biochemical pathways, potentially generating (relatively) specific dependencies on one or the other amino acid, vitamin, or fatty acids (15, 95). Theoretically, this offers the possibility of a new type of precision oncology in which the whole organism is deprived of specific micronutrients to exploit metabolic vulnerabilities of cancer cells without compromising the function of other essential cell types, including immune cells that should keep the tumor under control (96). Obviously, it poses a logistic problem to prepare close-to-synthetic diets lacking specific micronutrients (such as specific amino acids like asparagine plus glutamine; arginine; branched-chain amino acids including leucine, isoleucine, and valine; cyst[e]ine; methionine; serine, etc.; refs. 95, 97), rendering their practical application costly and unpleasant. Thus, in spite of rampant literature on the cancer growth–suppressive effect of the depletion of specific amino acids from the diet of mice, no translation into clinical trials has been attempted. From this point of view, the administration of enzymes that selectively destroy amino acids (as exemplified by parenteral administration of L-asparaginase, PEGylated argininase, L-cyst(e)inase deiminase for the depletion of asparagine, arginine, and cyst(e)ine, respectively) for the treatment of cancer constitutes a welcome alternative, though usually outside of the realm of nutritional interventions (95, 97). Several trials are under way using PEGylated argininase, which is administered in a parenteral fashion. Only in a few cases, such enzymes have been administered orally, as exemplified by methioninase (ref. 69; Supplementary Table S1).

Supplementation of an array of different vitamins and oligoelements, often in the form of polyvitamins, has been widely explored in clinical trials through a large panel of different malignancies, mostly yielding disappointing results (98). Cancer patients often turn to alternative medicine guided by social media as well as uninformed practitioners. Most frequently, patients use polyvitamin pills and so-called antioxidant supplements (usually containing vitamins A, C, and E, carotenoids, and coenzyme Q10) and oligoelements (such as ferrous supplements) that, according to some observational studies, have clear negative effects, for instance by increasing the rate of recurrence of breast cancer after chemotherapy (99). Moreover, large phase III trials such as the SU.VI.MAX trial (>12,000 patients) failed to demonstrate a reduction in overall cancer incidence after antioxidant supplementation (100). As a result, patients should be carefully advised NOT to take such supplements without specific instructions to do so. That said, there is a strong rationale in favor of the use of

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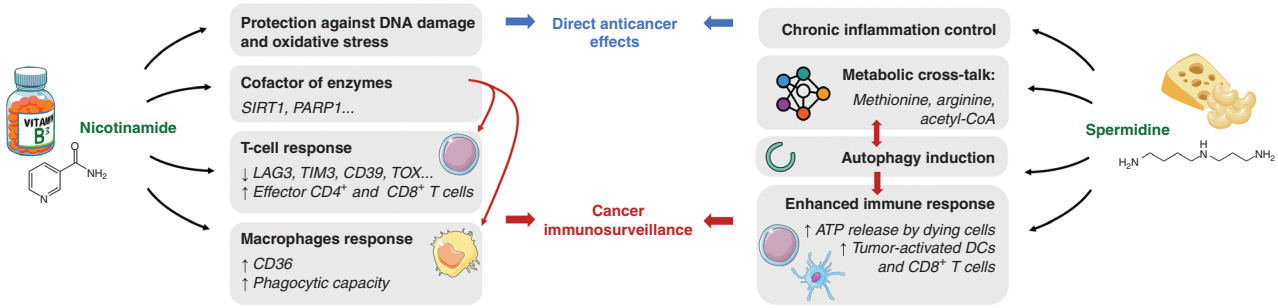

Figure 3. Anticancer effects of nicotinamide and spermidine. Nicotinamide (NAM) protects against DNA damage and oxidative stress, while it improves cancer immunosurveillance, as indicated by an increase in effector T cells, downregulation of immunosuppressive receptors such as lymphocyte-activation gene 3 (LAG3) and T-cell immunoglobulin and mucin-domain containing-3 (TIM3), upregulated macrophage CD36 and phagocyosis. Spermidine affects arginine, methionine, and acetyl-coenzyme A (Acetyl-CoA), stimulates autophagy, and boosts the immunogenicity of dying cancer cells, thus enhancing cytotoxic and memory T-cell responses. ATP, adenosine triphosphate; CD36, scavenger receptor class B member 3; CD39, ecto-nucleoside triphosphate diphosphohydrolase; DCs, dendritic cells, PARP1, poly(ADP-ribose) polymerase 1; SIRT1, sirtuin 1; TOX, thymocyte selection-associated high mobility group box protein.

specific micronutrients for the prevention and treatment of some types of cancers. It is important to note that, in most cases, the doses of vitamins required for anticancer activity are higher than the daily recommended dose needed for the avoidance of hypovitaminosis. Hence, the antineoplastic effects of vitamins usually cannot be explained by the reversal of a vitamin deficiency but, in most cases, rather must be attributed to supraphysiological, drug-like effects.

Amino Acids

Dietary L-glutamine supplementation has been demonstrated to sensitize mouse melanoma to BRAF inhibition. This effect has been attributed to an increase in its downstream metabolite α-ketoglutarate, which drives hypomethylaton of histone H3K4me2, thereby epigenetically suppressing oncogenic pathways (101). Intracellular α-ketoglutarate also mediates tumor suppression in mouse models of PDAC and colorectal cancer (102, 103). Parenteral L-glutamine supplementation has been shown to increase overall survival in patients with nasopharyngeal cancer under chemoradiotherapy (104). In mouse models, methionine supplementation improved the function of intratumoral T cells boosting spontaneous and immunotherapy-induced immunosurveillance, correlating with an increase in T-cell histone methylation and STAT5 in T cells. Indeed, tumor cells tend to overexpress the methionine transporter SLC43A2, thereby consuming methionine that becomes rate-limiting for T-cell metabolism (105). However, there is no available evidence that this strategy would improve the efficacy of cancer immunotherapy in patients.

Vitamin A

In humans, nutritional uptake of vitamin A (retinol, retinal, and retinoic acid) and its provitamins (in particular ß-carotene) is associated with a modestly reduced risk of some cancers including NSCLC (106) and PDAC (107), but interventional trials for using vitamin A for cancer prevention have been disappointing. In contrast, pharmacologic doses of all-*trans*-retinoic acid (ATRA) have a strong differentiation-inducing activity on selected leukemia cell types. ATRA is used for the routine treatment of promyelocytic leukemia (108) and might be useful for the treatment of AML as well (109). Interestingly, β-carotene has turned out to act as a direct inhibitor of the NLRP3 inflammasome, illustrating an "off-target" effect unrelated to vitamin A metabolism that might contribute to its cancer-preventive effects (110). That said, there is no convincing evidence in favor of the use of vitamin A for the prevention or treatment of solid cancers.

Vitamin B3

Niacin and niacinamide, best known as nicotinamide (NAM), which together are referred to as vitamin B3, are precursors of nicotinamide–adenine dinucleotide (NAD^+) that acts as a cofactor and substrate of multiple enzymes, including SIRT1 and poly ADP-ribose polymerase 1 (PARP1). Precursors of NAD^+ including vitamin B and synthetic agents (such as nicotinamide riboside) have a broad effect on metabolic health and age-associated diseases in mouse models (111, 112). High vitamin B3 intake is associated with a reduced risk of hepatocellular carcinoma in humans (113). Phase III clinical trials demonstrate the efficacy of NAM in the chemoprevention of nonmelanoma skin cancer (114) or as an adjunct to radiotherapy against bladder and laryngeal cancers (115, 116). Of note, NAM supplementation has chemopreventive effects against hormone-induced luminal B breast cancer in mice and increases the efficacy of anthracycline-based chemotherapy against breast cancer and fibrosarcoma (6). In mouse models, NAM also synergizes with gemcitabine against PDAC (117), and niacin favorably interacts with temozolomide against glioblastoma (118). These findings plead in favor of a broad anticancer activity of vitamin B3.

To explain its cancer-preventive effects (Fig. 3), it has been suggested that NAM directly protects skin cells against UVB irradiation-induced oxidative stress and DNA damage (119). However, beyond such cancer cell-autonomous effects, it appears plausible that NAM also (and perhaps preponderantly) acts on the immune system. Indeed, in immunodeficient mice lacking T cells or the type-1 interferon receptor, NAM loses its chemopreventive effects against hormone-induced breast cancer (114). When added to human peripheral blood mononuclear cells in a repeated fashion, NAM

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inhibits the expression of several immunosuppressive factors, e.g., the transcription factor TOX (which induces T-cell exhaustion) and several inhibitory receptors (such as CD39, TIM3, and LAG3). NAM also favors the differentiation of $CD4^+$ and $CD8^+$ T lymphocytes into effector memory and terminal effector T cells (120). As compared with circulating human T lymphocytes, T cells infiltrating human ovarian cancers express lower levels of NAM phosphoribosyltransferase (NAMPT), the enzyme that converts NAM to NAM mononucleotide (NMN) to enable the biosynthesis of NAD^+, and this may explain T-cell exhaustion because direct NAD^+ supplementation ameliorates tumor cell lysis by T lymphocytes *in vitro* (121). When injected into immunodeficient mice bearing a human CD19-expressing leukemia, NAM increases the intracellular NAD^+ concentration and the tumor-killing activity of adoptively transferred human CAR-T cells specific for CD19. Moreover, in immunocompetent mice, NAM synergizes with PD-1 blockade to induce the T-cell infiltration and immune control of melanomas (121). Niacin also has effects on myeloid cells. Thus, it rejuvenates macrophage and microglia from aged mice, increasing their expression of the scavenger receptor CD36 and improving phagocytic capacity, likely through an effect on G protein–coupled receptor 109A/hydroxycarboxylic acid 2 receptor (GPR109A/HCA2; ref. 122). The activity of niacin against orthotopic glioblastoma involves increased macrophage infiltration of the tumors and is negated by depletion of circulating monocytes or interruption of type-1 interferon signaling in malignant cells (118). The combination of NAM and gemcitabine improves the local immunosurveillance of orthotopic PDACs in mice, reducing tumor-associated macrophages and MDSCs, but enhancing the infiltration by $CD4^+$ and $CD8^+$ T cells, as well as the formation of tertiary lymphoid structures within the tumor (118). Altogether, these results suggest that NAM improves the immune control of an array of different malignancies. However, at this point, the proximal target(s) of the immune effects of NAM have not been fully elucidated with respect to the cell type (T lymphocytes versus myeloid cells) and molecular pathways (action on surface receptors versus NAD^+ metabolism).

Vitamin B5

Pantothenic acid (vitamin B5), the precursor of coenzyme A (CoA), stimulates T-cell responses against cancer, likely by favoring the differentiation of $CD8^+$ cytotoxic T cells into IL22-producing Tc22 cells. In mice, periodic injections of vitamin B5 boost the efficacy of PD-L1–targeted cancer immunotherapy, and *in vitro* culture of T cells with CoA stimulates their antitumor activity (75). In a small cohort of melanoma patients, the plasma levels of vitamin B5 positively correlate with responses to PD-1–targeted immunotherapy (75). Similarly, in *Mycobacterium tuberculosis*–exposed individuals, positive skin tests to tuberculin correlate with circulating vitamin B5 levels (123). Hence, pending further confirmation, it appears plausible that vitamin B5 has immunostimulatory effects.

Vitamin B6

The B6 vitamers (pyridoxine, pyridoxamine, and pyridoxal) must be phosphorylated by the enzyme pyridoxal kinase (PDXK) to generate active vitamin B6, pyridoxal-5-phosphate (PLP), which then acts as the prosthetic group of multiple enzymes. A meta-analysis of observational studies enrolling close to 100,000 participants with cancer concluded that high nutritional vitamin B6 uptake (food only, without supplements) significantly reduces overall cancer risk by 22% and that high PLP levels (above median) reduce pan-cancer risk by 34% and that of gastrointestinal tumors by 44% (124). However, high vitamin B6 uptake is associated with an increased HCC risk (113).

A high PAr index (i.e., the ratio of 4-pyridoxic acid over the sum of pyridoxal + PLP), which measures vitamin B catabolism during inflammation, is associated with a significantly increased risk of developing NSCLC (125, 126). Of note, elevated expression of the PLP-generating enzyme PDXK in NSCLC is a positive prognostic marker (127). Indeed, in mice, vitamin B6 stimulates anti-NSCLC immune responses when combined with cisplatin (128). Both cell-autonomous and immunologic mechanisms have been invoked to explain the antineoplastic action of vitamin B6 in preclinical studies. The combination of pyridoxin supplementation and high PDXK expression sensitizes cancer cells to chemotherapy-induced apoptosis in a cell-autonomous fashion (127) but also increases the immunogenicity of cancer cells succumbing to cisplatin (129). Thus, the synergistic interaction between pyridoxin and cisplatin is lost in athymic mice, meaning that it requires T lymphocytes to be efficient (129).

In human NSCLC, high PDXK protein expression correlates with the infiltration by activated DCs expressing LAMP3 (also known as DC-LAMP; ref. 130). PLP deficiency compromises the enzymatic activity of sphingosine-1-phosphate lyase 1 (which may cause immunosuppression) and kynureninase (which may cause inflammation) and disrupts the Th1/Th2 balance in favor of an excessive Th2 response, suggesting that its supplementation should cause immunostimulation, inhibit inflammation, and favor Th1 responses (131). In colorectal cancer patients, PLP negatively correlates with several markers of inflammation including CRP, IL6, IL8, serum amyloid A, and TNFα (132), but positively correlates with overall survival (133). However, there is no formal proof that the activity of PLP-dependent enzymes affects carcinogenesis and tumor progression. As an indirect hint in this direction, it has been reported that a high 3-hydroxykynurenine:xanthurenic acid (HK:XA) ratio, which reflects the activity of the PLP-dependent enzyme kynurenine aminotransferase, is associated with a low risk of developing NSCLC (134).

Studies in which vitamin B6 was supplemented to patients usually have failed to demonstrate cancer-preventive effects (124). Moreover, vitamin B6 may even accelerate tumor progression in specific cases. For example, in human AML, malignant cells depend on vitamin B6, and inhibition of PDXK and PLP-dependent enzymes (such as glutamic-oxaloacetic transaminase-2 and ornithine decarboxylase) blocks AML cell proliferation (135). Hence, the cancer-modulatory effects of vitamin B6 require further scrutiny and are likely tumor type–specific.

Vitamin C

A large body of literature deals with putative cancer-preventive effects of vitamin C (ascorbate) uptake and

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supplementation. However, the results are largely disappointing, perhaps with the exception of a moderately reduced risk of developing NSCLC with higher dietary vitamin C intake but not vitamin C supplement (RR: 0.84; 95% CI, 0.71–0.99; refs. 136, 137). Vitamin C may mediate direct anticancer effects through the induction of oxidative stress and DNA methylation (138). Moreover, in preclinical models, high-dose injections of vitamin C stimulate anticancer immune responses and synergize with adoptively transferred T cells, as well as with immune-checkpoint inhibitors (139, 140). Indeed, vitamin C can stimulate IL12 production by human dendritic cells, thereby shifting naïve α/β $CD4^+$ T lymphocytes toward an IFNγ-producing T helper 1 phenotype, enhance the cytotoxic function of α/β $CD8^+$ T cells, and favor the expansion of, and IFNγ and TNFα production by, γ/δ T cells (141). Intravenous (but not oral) administration of high-dose ascorbate has a radiosensitizing effect, hence enhancing the progression-free survival of PDAC patients in a phase I trial with respect to historical controls from the same institution (142). In a randomized trial, a topical solution consisting of 30% ascorbic acid in 95% dimethylsulfoxide was more efficient than imiquimod for the treatment of basal cell carcinoma (143). Of note, all ongoing trials involving vitamin C supplementation for the treatment of cancer are based on its intravenous infusion rather than oral supplementation (Supplementary Table S1).

Vitamin D

Oral vitamin D supplementation causes a small but significant reduction in the risk (RR = 0.87; 95% CI, 0.79–0.96) of cancer mortality (but not cancer incidence), according to a meta-analysis of 10 trials (144). Accordingly, the OS and RFS of lung cancer patients were improved among vitamin D users compared with nonusers (HR = 0.83; 95% CI, 0.72–0.95 and HR = 0.79; 95% CI, 0.61–0.97; ref. 145). 25-hydroxyvitamin D3 (25(OH)D3) serum concentrations correlate with the clinical response of patients with *EGFR*-mutant lung adenocarcinoma to EGFR inhibitors, commensurate with the capacity of vitamin D to prevent EGFR inhibitor resistance coupled to epithelial–mesenchymal transition (EMT; ref. 146). In advanced colorectal cancer patients under chemotherapy, higher circulating 25(OH)D3 levels are associated with better progression-free (HR = 0.85; 95% CI, 0.71–0.99) and overall survival (HR = 0.56; 95% CI, 0.38–0.82; ref. 147). In a retrospective analysis of two independent cohorts of melanoma patients, vitamin D use was associated with a strongly decreased (by 64%–65%) risk of immune-checkpoint inhibitor-induced colitis (148), in line with prior reports of prophylactic use of vitamin D in ulcerative colitis determined in a phase III clinical trial (149). Thus, vitamin D can mitigate (nonspecific) colic inflammation without compromising the (specific) anticancer immune response. Of note, in a randomized trial, vitamin D supplementation (for a median period = 7.1 years; postintervention observation median = 13.8 years) has been shown to reduce the risk of *in situ* ductal carcinoma *in situ* of the breast (HR = 0.76; 95% CI, 0.61 to 0.94; ref. 150). This type of breast cancer is under strong immunosurveillance (151), evoking the possibility that vitamin D effects are not necessarily cancer cell autonomous.

Spermidine

Spermidine is a polyamine present in most food items, though at variable abundance, as well as in the gut microbiota. Because it can be synthesized by the human organism, it is not a vitamin. However, spermidine levels tend to decline with age, a finding that led to the speculation that spermidine supplementation might become necessary as organisms age and that spermidine hence would be an "age-dependent vitamin" (152). Reduced dietary spermidine intake has been correlated with an enhanced overall risk of cancer-related mortality (153), as well as with the specific risk of developing colorectal cancer (154, 155). In mice, oral spermidine supplementation reduces inflammation-induced colon cancer (156) and improves immunosurveillance in models of transplantable cancer responding to chemotherapy (48) or immunochemotherapy (49). This latter effect has been explained by the induction of autophagy in tumor cells, thus facilitating the release of ATP as a chemoattractant for dendritic cells, hence stimulating immunosurveillance (ref. 48; Fig. 3). However, thus far no clinical trials evaluating the impact of spermidine on cancer have been initiated.

Polyphenols and Other Plant-Derived Compounds

Numerous studies insist on the health-improving and anticancer effects of polyphenols contained in specific plants (for review see refs. 157 and 158). The mode of action of agents such as apigenin, curcumin, epigallocatechin gallate, quercetin, and resveratrol, has extensively been studied, though with the difficulty that such agents act on cells at comparatively high concentrations (>10 μmol/L), implying the engagement of multiple different molecular targets. Clinical studies using such polyphenols as food supplements (as well as other nonpolyphenols including indole-3 carbinol from cruciferous vegetables and lycopene from tomatoes) have been performed, though without any major success, perhaps linked to their poor bioavailability. This said, further research for natural anticancer agents present in healthy food items should be encouraged.

Marine Omega-3 Fatty Acids and Other Unsaturated Fatty Acids

The plasma concentrations of long-chain (20–22 carbon) omega-3 polyunsaturated fatty acids (eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids) are associated with reduced overall and cancer-related mortality (159). Although there is consensus that the replacement of red meat by fish and seafood has beneficial effects on human health, there are no studies showing that dietary supplementation of synthetic omega-3 polyunsaturated fatty acids would prevent cancer or improve the outcome of oncologic treatments. Moreover, the claim that omega-3 polyunsaturated fatty acids could be part of a so-called immunonutrition designed to improve immune responses is not convincingly substantiated by clinical trials yet. Several trials investigating omega-3 alone or in combination with additional food supplements are under way (Supplementary Table S1). Of note, preclinical results indicate that a specific unsaturated fatty acid, linoleic acid (but not oleic acid), suppresses T cell–mediated immunosurveillance (160). Hence, not all unsaturated fatty acids exert immunostimulatory functions.

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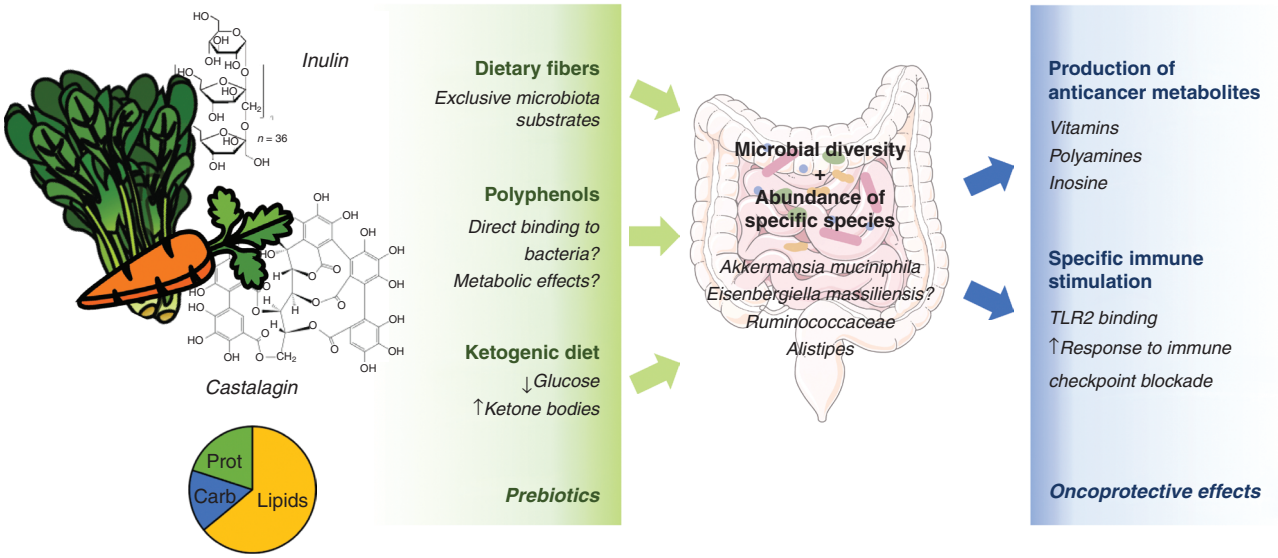

Figure 4. Microbiota-centered interventions. The microbiota is influenced by interventions on the quantity and quality of macronutrients, such as ketogenic diet, dietary fibers, and polyphenols. Specific bacteria in the gut may have oncoprotective effects on the production of specific metabolites and the stimulation of immunosurveillance, for instance, by the induction of crossreactive immune responses or by stimulation of Toll-like receptor 2 (TLR2). Note that the anticancer effects of *Eisenbergiella* are still hypothetical as indicated by the question mark. Prot, protein.

In synthesis, there is fragmentary evidence suggesting that supplementation with specific vitamins and other micronutrients improves the outcome of cancer treatments in preclinical models involving immunocompetent mice. In addition, clinical studies point to the potential utility of topical ascorbate, oral nicotinamide, and vitamin D supplementation for the prevention or treatment of specific malignancies. In contrast, the indiscriminate administration of polyvitamins should be considered as a non sequitur. Interventions on specific micronutrients are being investigated in multiple clinical trials for the prevention or treatment of neoplastic disease (Supplementary Table S1).

MICROBIOTA-CENTERED INTERVENTIONS USING PREBIOTICS

There is increasing awareness that nutritional interventions including dietary fibers and fermented foods affect the microbiota, which in turn affects organismal metabolism and influences immune status by multiple effects including the generation of B vitamins and polyamines (3, 161), as well as by eliciting specific immune responses against microbial antigens (ref. 162; Fig. 4). Indeed, clinical trials involving fecal microbial transplantation have shown the potential of improving cancer immunotherapy (163, 164), and supplementation with live *Chlostridium butyricum* has clinical efficacy against kidney cancer treated with immunotherapy, as demonstrated in a randomized phase I trial (165). Moreover, there is a broad consensus that broad-spectrum antibiotics administered to cancer patients shortly before or during immunotherapy have a negative impact on treatment outcome, underscoring the essential role of the microbiota in determining the immune tonus (3, 166). Logically, many research groups are attempting to identify immunostimulatory, health-improving bacteria that could be administered as live microorganisms or "probiotics," either as single (monoclonal) species or as a mixture of several (polyclonal) species (3). Ironically, cancer patients tend to self-medicate with over-the-counter probiotics, which may colonize the gut causing a reduction in the ecological diversity of the microbiota, as well as signs of dysbiosis. Especially, if combined with a diet poor in fibers, this correlates with reduced responses of melanomas to PD-1 blockade in patients and mice (167, 168). Here, we will only discuss the dietary use of "prebiotics," i.e., orally administered compounds that are supposed to induce the growth or activity of beneficial microorganisms.

Favorable nutritional patterns including the ketogenic diet increase the abundance of *Akkermansia muciniphila* in the human gut microbiota (169, 170). *A. muciniphila* is a bacterium that has broad antiaging, anti-inflammatory, antiobesity, antidiabetic, and colon cancer–preventive effects in mice (171, 172), as well as antidiabetic effects in obese human volunteers (173). The presence of *A. muciniphila* in the gut correlates with the response of NSCLC patients to PD-1/PD-L1–targeted immunotherapy (174), and gavage of *A. muciniphila* to mice significantly improves immunotherapy responses (175). Such effects may be related to its capacity to enhance the production of polyamines and other favorable metabolites in the gut (176), as well as to the stimulation of Toll-like receptor-2 (TLR2) by specific ligands (177). Another potentially interesting bacterium is *Eisenbergiella massiliensis*, which increases in mice under a ketogenic diet, as well as in humans undergoing a carbohydrate-low-diet intervention, correlating with circulating 3-hydroxybutyrate concentrations (51). Hence, it is possible that the ketogenic diet mediates its effect at least in part indirectly, via effects on the gut microbiota.

Epidemiologic association studies provide overwhelming evidence in favor of the cancer-preventive and disease-

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attenuating effects of dietary fibers, which apparently protect against multiple different types of cancer including those affecting bladder (178), breast (179), colon (180), liver (181), ovary (182), and pancreas (183). A number of dietary clinical interventions have been performed to increase the ingestion of nonabsorbable dietary fibers, usually by gross interventions, such as shifting from a Western style to a Mediterranean or vegan diet or the administration of navy beans or heat-stabilized rice bran. Although the results of many of these trials are positive, they are difficult to interpret due to the fact that they did not involve the administration of pure fiber preparations. Indeed, very few studies are based on the administration of chemically defined fibers such as inulin, which causes major shifts in the human microbiota (184). In a randomized double-blinded trial, colorectal cancer patients received 30 g of synthetic fibers (composed of fructooligosaccharide, xylooligosaccharide, polydextrose, and resistant dextrin, each 25%) during the perioperative period, causing an increase in immunostimulatory bacteria (*Bacteroidetes*, *Bifidobacterium*, and *Enterococcus*) in the gut (185). However, thus far no results from interventional trials are available to demonstrate that defined fibers would have cancer-preventive or cancer therapy–enhancing effects in patients. Several trials are evaluating the potential anticancer effects of oligo-fucoidan (sulfated polysaccharides) or other chemically defined fibers (Table 2).

Of note, defined polyphenols may mediate interesting probiotic effects. Polyphenol-enriched diets and decoctions have been shown to alter the gut microbiota in a favorable fashion, reducing signs of intestinal permeability in elderly patients (186). However, the precise molecular nature and mode of action of such polyphenols have not been defined. As a notable exception, the ellagitannin polyphenol, castalagin, which is contained in a Brazilian berry, has recently been found to mediate specific effects on the microbiota. When mice are fed with castalagin, bacterial species belonging to the *Ruminococcaceae* and *Alistipes* families become more abundant (187). These species are indeed associated with favorable immunotherapeutic responses in melanoma patients and improve the outcome of immunotherapy in mice (188). Castalagin actually binds to a *Ruminococcus* species and promotes anticancer immune responses in mice (187). Hence, castalagin might be taken advantage of as a prebiotic that favors the expansion of immunostimulatory bacteria. Interestingly, castalagin is metabolized to urolithins, including urolithin A (187), which reportedly stimulates mitophagy (189) and mediates positive effects on human health (190). Hence, the question comes up whether it would be possible to replace castalagin with urolithins.

CONCLUSIONS

Popular and social media are plagued with reports on the close-to-miraculous short-term effects of specific diets and "superfoods" that are praised for their health-preserving and -improving virtues, though with little empirical bases and no scientific grounds. In the present article, we have summarized some of the current knowledge on science-driven nutritional interventions on cancer, placing particular emphasis on the identification of specific molecular entities contained in food that may improve the clinical manifestation and progression of malignant disease, while neglecting the impact of nutritional interventions on subjective well-being, treatment-induced side effects, and palliative aspects.

In a certain sense, it appears that the most important dietary recommendation that can be given to the public including cancer patients is the avoidance of an intrinsically toxic Western-style diet characterized by the hypercaloric ingestion of refined sugars, ultraprocessed food items, and red meat, as well as by the lack of fresh fruit, vegetable, whole grain, fibers, and fish. As a first step into the right direction, CR may be attempted following constant, cyclic, or intermittent schedules. As a second step, the suppression of excessive carbohydrates and sugars ("carbotoxicity") may help reduce food addiction and favor weight loss. Unfortunately, any major switch in the dietary pattern poses the problem of low patient compliance requiring specific countermeasures which could include the provision of standardized meals in a supervised environment, as well as frequent metabolomic monitoring of patients using mass spectrometric methods or nuclear magnetic resonance.

Recently, the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide has been FDA approved for the pharmacologic treatment of obesity (191). It will be important to determine whether weight reduction that can be achieved with such GLP-1 agonists [or new drugs such as tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist (192), as well as with new drug combinations such as semaglutide plus cagrilintide, a long-acting amylin analogue (193)] improves the oncological management of initially obese patients. Indeed, it remains to be determined whether a mere reduction of adiposity due to the appetite-controlling effects of GLP-1 agonists without substantial changes in diet composition would improve immunosurveillance. Most likely, the combination of a healthy (non–Western style) diet with appetite-controlling drugs will yield synergistic results.

There are only a few defined nutrition-relevant molecules that emerge as potential anticancer effectors. Beyond ketone bodies (that are induced by ketogenic diets, yet can also be administered as food supplements), most of these potentially antineoplastic molecules are vitamins, perhaps reflecting the historical (and mostly false) idea that vitamin supplementation would promote health. This assumption likely favored in-depth research into the question of whether vitamins can be used for cancer prevention or treatment. However, to our knowledge, nicotinamide (vitamin B3) and vitamin D are the only molecules that have been shown to possess cancer-preventive effects (against skin cancer and mammary *in situ* ductal carcinoma, respectively) in randomized clinical trials (114, 150). Importantly, when vitamins mediate anticancer effects, they often do so at relatively high doses, which are well superior to those required for the palliation of hypovitaminosis.

Although laymen are constantly exposed to reports on the power of plant-derived molecules, in particular polyphenols contained in fruit and vegetable, and in spite of an extensive scientific literature on this subject, very few if any such molecules have demonstrated clinical utility. This strongly contrasts with the historical identification of antineoplastic

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drugs (exemplified by camptothecin, epipodophyllotoxins, taxanes, and vinca-alkaloids) from poisonous plants (194). Such cytotoxicants were purified based on their bioactivity. In sharp contrast, specific compounds, in particular polyphenols, have been isolated from nonpoisonous food items based on other criteria, usually physicochemical properties facilitating their tracing, in particular colorfulness and antioxidant activity. Such nonpoisonous compounds that are praised in the scientific and popular literature are relatively abundant (implying that nonabundant molecular species have been less studied) and are endowed with reduced bioavailability. Thus, they are scarcely absorbed in the intestine (e.g., curcumin) or are submitted to effective biochemical modification/detoxification in the enterohepatic cycle (e.g., resveratrol), precluding major drug-like effects on the mammalian organism.

Although many of the polyphenols have been shown to mediate cytostatic and cytotoxic effects on cultured tumor cells *in vitro*, they failed to act on cancers in real-life situations, in the living organism, underscoring the importance of the "ecological view" of cancer. That said, it is still possible that low-abundant molecular species contained in health-related food items favorably influence the tumor-related ecosystem, hence dampening procarcinogenic inflammation and stimulating anticancer immunosurveillance. To identify such low-abundant molecules, it will be necessary to constitute chemical libraries using modern methods of chromatographic fractionation and mass spectrometry. Such libraries could be screened with the scope of discovering molecular entities that act on malignant cells as well as on other cancer-relevant cell types composing the tumor-relevant ecosystem. Of note, specific molecules contained in healthy food items may act as probiotics, hence stimulating the intestinal proliferation of immunostimulatory bacteria and illustrating a highly indirect mode of action.

Personalization may be yet another challenge for nutritional interventions on cancer, exactly as this is the case for current pharmacologic treatments. Thus, depending on the physical state of the patient, the enterotype, the specific molecular genetic (and metabolic) properties of the cancer, as well as on surgical, radiologic, cytotoxic, or immunotherapeutic treatments, distinct dietary interventions may be required to facilitate wound healing, reduce the toxicity of the treatment, or improve the efficacy of the cancer-immunity dialogue. With respect to the latter, several dietary interventions such as fasting, ketogenic diet, immunostimulatory bacteria, and administration of β-hydroxybutyrate or castalagin improve the efficacy of PD-1 blockade in mouse models (195). However, these preclinical observations have not yet been translated into medical practice.

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Note

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