Nutrition, inflammation and cancer

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Quantitative and qualitative aspects of nutrition have a profound effect on leukocytes and thereby affect proinflammatory carcinogenic effects or anticancer immune responses. As a result, nutrition affects the incidence, natural progression and therapeutic response of malignant diseases, both in humans and in preclinical animal models. Here we discuss the molecular mechanisms through which alimentary cues modulate metabolic, microbial and neuroendocrine circuitries and thus affect the probability of developing premalignant lesions that progress to clinically manifested disease and the response to therapeutic intervention. We examine each of the connections that compose the triangle of nutrition, immunological and inflammatory reactions and cancer while focusing on the mechanistic aspects of these relationships.

People with cancer often rationalize their disease as being a consequence of adverse life experiences; however, large population studies have not established such a correlation[1]. In sharp contrast, there is overwhelming epidemiological evidence that dietary factors, particularly those that result in overweight and obesity, influence morbidity and mortality in multiple distinct cancers[2]; however, this connection is often denied at the individual, subjective level. Indeed, the causal link between overnutrition or imbalanced nutrition and cancer is obfuscated for multiple reasons.

First, at the population level, overnutrition and imbalanced diets are typically associated with other health-compromising factors that include, but are not limited to, consumption of tobacco and alcohol, decreased physical activity and exposure to environmental toxicants, all of which not only are established risk factors for cancer development but also are linked to poor education and low income. Low socioeconomic status is yet another independent risk factor for premature mortality, including death from cancer[3]. Hence, it is intrinsically difficult to 'isolate' dietary risk factors in epidemiological studies. That being said, careful experimentation in rodents has irrefutably demonstrated the influence of nutrition on cancer development[4].

Second, in contrast to continuous variables, such as blood pressure or glucose concentrations, cancer occurs as an all-or-nothing phenomenon, as the clinical manifestation of stochastic events influenced by the number of stem cell divisions[5] and a debatable degree of 'bad luck' due to hazardous mutations, as well as avoidable causes associated with lifestyle factors[6]. Undoubtedly, the most important intrinsic risk factor in cancer is old age, thus suggesting that measures that slow down the aging process, such as caloric restriction, or that accelerate aging, such as overnutrition[7], have large effects on the incidence of cancer; without these effects, there might be a direct cause-and-effect relationship between unhealthful behavior and carcinogenesis. Unsurprisingly, common risk factors determine the incidence of neoplastic and cardiovascular diseases[8]. Hence, many effects of nutrition on the development and progression of cancer lack 'specificity' in their association, and such alimentary cues also affect the risk of developing metabolic syndrome, a prelude to arteriosclerosis and neurodegeneration (**Fig. 1**).

Third, the relationship between diet and cancer is not as linear as those between UV light and melanoma, or between tobacco use and lung cancer (perhaps with the exception of orally available chemical mutagens in tobacco that directly cause gastrointestinal cancers[9], which will not be discussed here). In general, nutrition affects cancer development somewhat indirectly. For example, the microbiome can be affected by changes in carcinogenic or tumor-suppressive metabolites and microbe-associated molecular patterns generated in the gut[10]; endocrine factors, such as concentrations of circulating insulin, insulin-like growth factor, leptins and adiponectins[2]; and inflammatory and immunological parameters, which are interrelated because the same leukocyte populations contribute to both inflammation and immune responses.

In this Review, we focus on the complex relationships among nutrition, inflammation–immunity and cancer. We examine each side of this triangle separately (**Fig. 1**) and provide a unifying hypothesis of how nutritional imbalances may affect the development and progression of cancer.

Inflammation, immunity and cancer

Although the relationship between chronic inflammation and cancer ('the wound that never heals') has long been acknowledged[11], the idea that cancer is under immunosurveillance has only recently gained broad acceptance[12]. One conceptual difficulty that has been (and remains) difficult to resolve is that many of the leukocyte subsets and factors that govern inflammation also influence immune reactions,

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and vice versa. For example, inflammasomes serve a dual role in inflammation and immunity and thus favor or suppress tumorigenesis in a highly context-dependent fashion. The ambivalent contribution of inflammasomes to carcinogenesis and immunosurveillance is most probably based on the existence of a variety of distinct inflammasome complexes and inflammasome products that are expressed differentially in tissues and cell types in an activation-state-dependent manner[12–14].

Chronic inflammation is carcinogenic, as exemplified by reflux esophagitis, gastritis, inflammatory bowel disease, silicosis-associated lung cancer, asbestosis-induced mesothelioma and various types of hepatitis induced by viruses, alcohol consumption or a Western-style diet[11]. The carcinogenic effects of inflammation may be dependent on chronic stimulation of cellular turnover, with a consequent increase in stem-cell divisions, as well as on local mutagenic effects. Mutagenesis may be promoted by the inflammation-causing agent itself and by enhanced production of reactive oxygen species that either are a side product of locally enhanced metabolism or are generated specifically by macrophages[15]. In addition, unresolved inflammation favors trophic interactions between parenchymatous cells and infiltrating leukocytes as it antagonizes immunosurveillance. As an example, alternatively activated (M2) macrophages and granulocytes can act as myeloid-derived suppressor cells within incipient tumor lesions[16]. Similarly, the cytokine TGF-β, which has a major role in fibrotic reactions, is also a major local immunosuppressor[17].

The relationship between neoplasia and the immune system has been didactically condensed into the '3E hypothesis', which involves initial elimination of transformed cells by immunological effector cells; subsequent equilibrium between malignant cells and the immune reaction within a smoldering (and mostly indolent) neoplastic lesion, and final escape of cancer cells from immunological control[18]. That final event, which is linked to clinical disease manifestation, often after a long latency, can involve the selection of nonimmunogenic cancer cells (immunoediting) or active suppression of the local immune response (immunosubversion)[18,19]. Successful treatment of cancer with chemotherapy or radiotherapy reestablishes the equilibrium state by reactivating immunosurveillance, usually by increasing the immunogenicity of cancer cells, which release danger-associated molecular patterns, and/or by depleting immunosuppressive leukocytes such as myeloid-derived suppressor cells and regulatory T cells from the tumor bed[20,21]. Similarly, immunotherapy with immunological-checkpoint blockers reactivates anticancer responses mediated by exhausted T cells, provided that such cells are already present in the tumor immune-cell infiltrate[22,23].

Distinguishing between protumorigenic effector cells and anticancer effector cells in the local leukocyte infiltrate requires accurate phenotyping of various cell types (to distinguish myeloid cells with differing polarities as well as distinct T lymphocyte populations that may have regulatory and effector functions) through multicolor immunohistochemistry, cytofluorometric analysis of monocellular suspensions[24] or single-cell transcriptomics[25]. The single-cell-transcriptomics approach has an advantage in that it reveals the T cell repertoire of infiltrating T lymphocytes and thus yields clues as to their possible specificities. Additional techniques might involve the *ex vivo* culture of tumor slices[26] or oligocellular preparations, the addition of immunostimulators or checkpoint blockers, and final quantification of cytokines, T cell–activation markers or immune-cell trajectories[27].

Nutrition, inflammation and immunity

Awareness that nutrition influences inflammatory and immune responses has led to the development of the 'dietary inflammatory
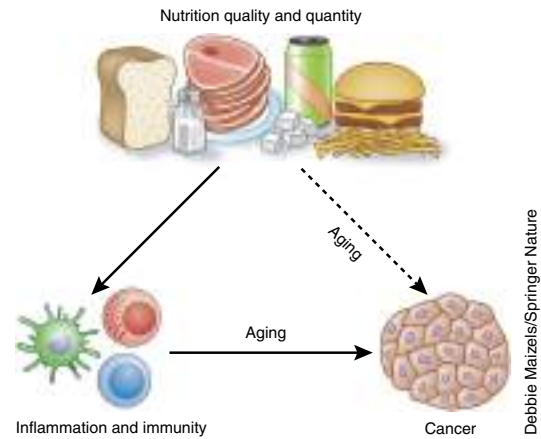

Figure 1 Relationships among nutrition, inflammation and immunity, and cancer. The triangle composed of nutrition, inflammation and immunity, and cancer illustrates how qualitative and quantitative imbalances in food intake predispose organisms, in a manner dependent on or independent of the immune system, to a time-dependent deterioration in function that culminates in the development and progression of cancer. Image adapted from Servier Medical Art (http://www.servier.com/Powerpoint-image-bank/) under the terms of the CC BY 3.0 license.

index'[28] and the use of terms such as 'immunonutrition'[29] in epidemiological and clinical studies. Nonetheless, the effects of individual macro- and micronutrients on leukocyte function have not been studied in great molecular detail, perhaps with the exception of hypovitaminoses. At present, strong immunomodulatory effects have been revealed for quantitative variations in nutrient uptake, particularly in overeating and fasting (**Fig. 2**).

Hyperadiposity is linked to chronic subclinical inflammation through a variety of mechanisms[30]. Obesity is associated with a switch in the phenotype of adipose-tissue macrophages from the M2 anti-inflammatory phenotype to a so-called 'M1 proinflammatory' phenotype; enhanced production of multiple proinflammatory cytokines, such as TNF and the interleukins IL-6 and IL-1β; an elevation in glucose and free fatty acids, leptin, insulin and the insulin-like growth factor IGF1; a decrease in adiponectin; and intestinal dysbiosis with diminished barrier function, which favors endotoxinemia and overrepresentation of bacterial species producing procarcinogenic metabolites[2,31]. Saturated free fatty acids promote inflammation by binding to the Toll-like receptors TLR4 and TLR2 through the adaptor protein fetuin 1 and consequently activating proinflammatory factors such as NF-κB and JNK1 (ref. 32). Obesity is also linked to systemic inhibition of autophagy as a result of high intracellular concentrations of acetyl coenzyme A[33,34], elevated trophic signaling that results in activation of the metabolic checkpoint kinase mTOR and, in some organs such as the liver, down-regulation of the proautophagic ATG7 protein[35]. The subversion of autophagy results in a decrease in the cytoplasmic recycling of damaged organelles, with consequent acceleration of the aging process[7], accumulation of potentially oncogenic products such as SQSTM1 (best known as p62)[36] and uninhibited activation of the NLRP3 inflammasome[37]. Interestingly, a high-fat diet stimulates generation of the complement fragment C5a, even in mouse strains that are resistant to obesity induced by such a diet, and this sign of complement activation has been causally linked to high-fat-diet-triggered intestinal inflammation and accelerated carcinogenesis in *Apc*[Min/+] mice, a genetic model of spontaneous intestinal tumorigenesis[38].

Obese people exhibit many immunological abnormalities also associated with old age[39], in line with the proposal that obesity accelerates
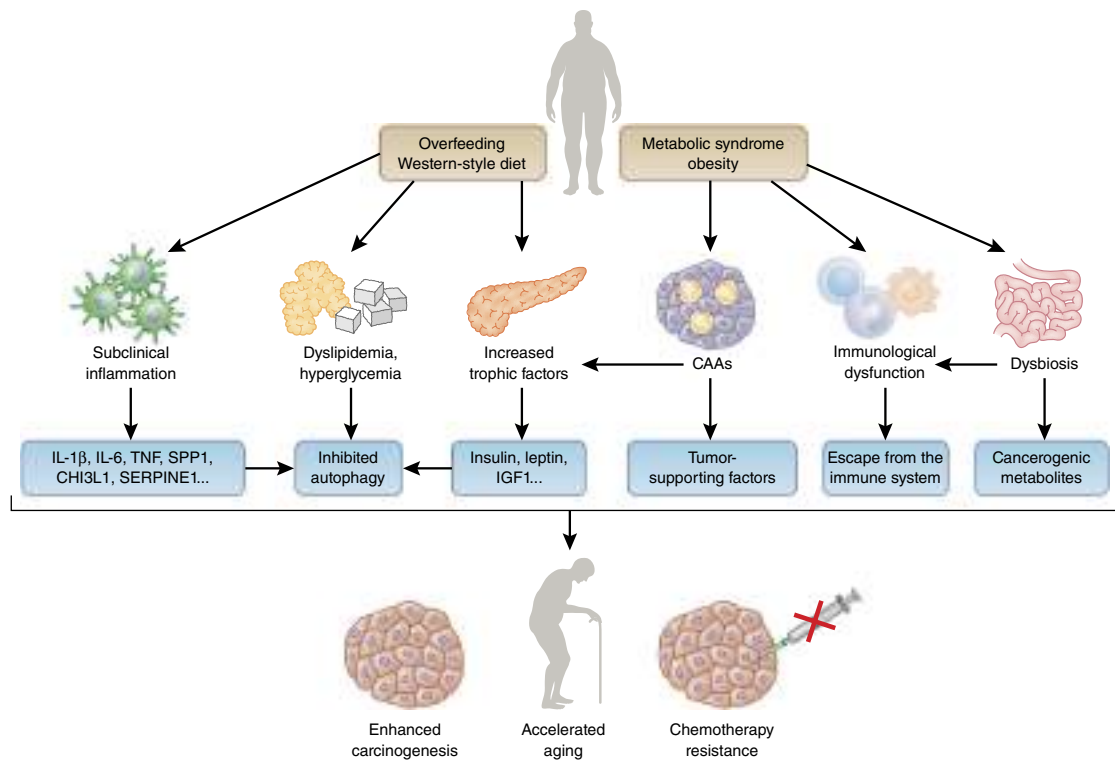
Figure 2 Pathophysiological mechanisms that link nutrition to carcinogenesis, aging and resistance to chemotherapy. Genetics or lifestyle-driven changes in body composition (e.g., overfeeding or a Western-style diet) result in a prepathological phenotype (metabolic syndrome) or pathological phenotype (obesity); these phenotypes together accelerate cellular transformation, aging and resistance to anticancer treatments, through multiple mechanisms. Elevated nutrient intake favors the generation of a subclinical inflammatory status with a consequent increase in circulating proinflammatory cytokines; determines the excessive increase in circulating glucose and lipid concentrations; and increases the levels of trophic hormones. Together those alterations produce a vicious cycle that leads to inhibition of autophagy and satisfies the metabolic needs of cancer cells. In addition, stromal cancer-associated adipocytes (CAAs) feed that circuitry and support tumor progression. Alternatively, an excess of nutrients can subvert immunological function, either directly or indirectly, through modification of the composition and metabolism of the intestinal microbiota. Such aberrations render the tumor microenvironment immunosuppressive and impair the therapeutic response to anticancer agents. CHI3L1, chitinase 3-like 1; SPP1, secreted phosphoprotein 1; SERPINE1, Serpin family E member 1. Image adapted from OpenClipart (https://openclipart.org/) under the terms of the CC0 1.0 license.

aging[7]. Thus, obese people have fewer cytotoxic CD8+ T cells[40], perhaps as a consequence of hastened thymic atrophy[41] or diminished dendritic-cell function[42]. Moreover, obesity is associated with a decreased number and function of natural killer cells, as well as with a substantial decrease in circulating $V_\gamma 9^+ V_\delta 2^+$ T cells[43]. Experimental anticancer immunotherapies that work in lean mice might fail in[44] or be toxic to[45] obese mice. Thus, the lethal cytokine storm that manifests in obese mice after immunostimulation with antibody to the costimulatory receptor CD40 and with CpG dinucleotides has been attributed to enhanced production of TNF by adipose-tissue macrophages[45]. Together, these findings support the importance of considering information about body weight during the clinical development of immuno-oncology drugs.

Fasting has considerable anti-inflammatory effects that are clinically exploited in some countries, such as for the treatment of rheumatoid arthritis. A 24-hour period of fasting *in vivo* has been shown to decrease the *in vitro* lipopolysaccharide-induced NLRP3-inflammasome-dependent production of IL-1β by monocytes from human volunteers[46]. This effect has been linked to activation of the energy biosensor sirtuin-3, a deacetylase. Notably, the starvation-induced inhibition of IL-1β production is lost only 3 hours after refeeding of a hypocaloric (500-kcal) meal[46], thus suggesting that such inhibition is highly sensitive to even small variations in nutrient uptake. Fasting also

causes protein hypoacetylation and signs of autophagy in circulating peripheral blood mononuclear cells from human volunteers[47]; hence, the observed inhibition of NLRP3 inflammasomes might be related to autophagy induction.

In mice, fasting increases resistance to infection with *Listeria monocytogenes* or to injection of the TLR4 ligand lipopolysaccharide. This beneficial effect of fasting, which is subverted by intraperitoneal injection of glucose and can be mimicked by therapeutic blockade of glucose use via 2-deoxy-D-glucose, has been explained by an increase in ketone bodies (described below). However, this effect is not linked to a decrease in the production of proinflammatory factors such as IL-6 and TNF[48]. In contrast, fasting or treatment with 2-deoxy-D-glucose sensitizes mice to infection with vaccinia virus or to injection of the synthetic RNA duplex poly(I:C)), a ligand of TLR3, thereby resulting in increased death[48].

Thus, the feeding state appears to have a substantial effect on inflammatory and immune responses. Indeed, even in lean mice, feeding causes a physiological increase in circulating IL-1β that has been attributed to the action of the microbiome and increased glucose concentrations in peritoneal macrophages and that might contribute to postprandial stimulation of insulin secretion[49]. However, beyond physiology, spontaneous changes in feeding behavior—such as sickness-associated anorexia, which is often triggered by infections or severe

disease—might be an evolutionarily conserved defense strategy for decreasing excessive inflammation and improving immune responses, such as by increasing autophagic flux[50] (**Fig. 3**).
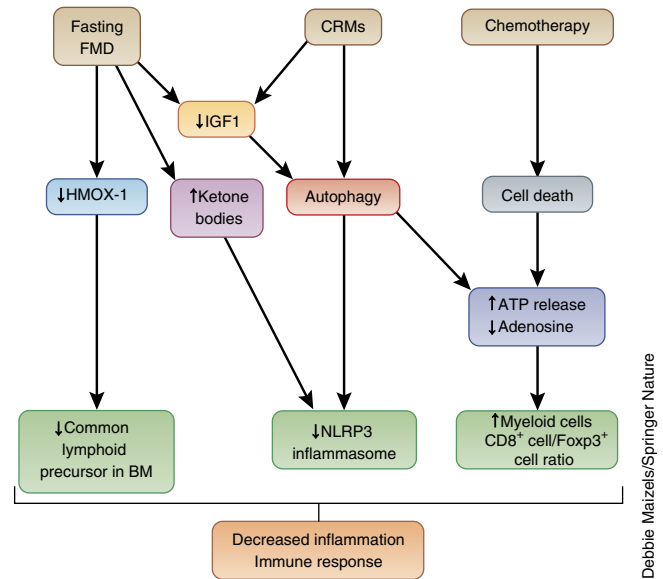
A high-fat, adequate-protein, low-carbohydrate diet causes a decrease in circulating glucose concentrations together with an increase in free fatty acids and ketone bodies, such as acetoacetate and β-hydroxybutyrate. Collectively, these changes also occur after fasting or exercise[51]. The ketone body β-hydroxybutyrate is highly efficient in inhibiting the NLRP3 inflammasome, but not the NLRC4 inflammasome, by preventing cytosolic potassium influx and consequent formation of aggregates consisting of the adaptor ASC and the NLRP3 inflammasome[52]. Notably, the beneficial effects of fasting on bacterial infection and lipopolysaccharide-mediated toxic shock are mediated by ketone bodies[48], although it has not been determined whether these effects involve inhibition of the NLRP3 inflammasome with a consequent decrease in IL-1β. Beyond its effects on the NLRP3 inflammasome, β-hydroxybutyrate is an endogenous ligand of the G-protein-coupled receptor GPR109A (HCAR2), which is abundantly expressed by monocytes and macrophages and has anti-inflammatory effects[51]. Hence, ketone bodies dampen inflammation through several mechanisms (**Fig. 3**).

Nutrition and cancer epidemiology

Obesity will probably become the most important avoidable risk factor for malignancy, before tobacco, and it has been demonstrated to affect the incidence and progression of various solid cancers[53]. Obesity concurrent with metabolic syndrome appears to be more closely associated with cancer than is obesity concurrent with 'metabolic health'[54]. Hence, distinguishing different types of obesity, rather than focusing exclusively on the body mass index, appears to be crucial, given that central obesity with 'preferential' accumulation of visceral fat and a consequent increase in waist circumference is associated with the highest incidence of metabolic syndrome. Metabolic syndrome–associated factors, such as high blood pressure and circulating C-reactive protein, glucose, IL-6, insulin, leptin and triglycerides—in contrast to low adiponectin and high-density-lipoprotein cholesterol—are associated with the presence of macrophages that form crown-like structures in the breast tissue, which are considered to be a sign of white-adipose-tissue inflammation and a marker of poor prognosis[55]. In mice, obesity-driven breast-cancer progression requires the NLRC4 inflammasome, and expression of *NLRC4* mRNA in noncancerous human breast tissue indeed correlates with body mass index and is high in mammary carcinomas[56]. Such findings underscore the strong relationship between metabolism and procarcinogenic inflammation.

Beyond the unquestionable links among quantitative overnutrition, inflammation and elevated cancer risk, epidemiological studies have linked cancer to qualitative disequilibria in food composition that have been tentatively condensed into unidimensional numeric values. Thus, the 'dietary inflammatory index' weights each major macronutrient and multiple micronutrients on the basis of their general proinflammatory effects, as measured, for example, by assessment of C-reactive protein in serum[28]. This index significantly correlates with the risk of developing postmenopausal breast cancer[57], colorectal cancer[58] or lung cancer in smokers[59], among other examples. Alternative scores, such as the 'Mediterranean diet score' and the 'healthy eating index', have also been associated with the risk of developing colorectal cancer[60].

Micronutrients with anticancer properties include some vitamins. For example, high dietary intake of dietary vitamin B6 (pyridoxine) and high plasma concentrations of its metabolite, PLP (pyridoxal-5′-phosphate), are associated with a general decrease in cancer risk, particularly in gastrointestinal cancers[61]. In mouse models, pyridoxine stimulates the anticancer immune response in the

Figure 3 Immune-system-mediated effects of fasting and caloric-restriction mimetics in anticancer therapy. Fasting or a fasting-mimicking diet (FMD) and caloric-restriction mimetics (CRMs) elicit an anticancer immune response through convergent mechanisms. A decrease in circulating concentrations of IGF1 and the activation of autophagy promote an increase in precursors of CD8+ T lymphocytes, mediated by heme oxygenase 1 (HMOX-1), in the bone marrow (BM) and less release of immunostimulatory ATP from tumor cells. When combined with cytotoxic chemotherapeutic agents, fasting and caloric-restriction mimetics modify the tumor immune-cell infiltrate. Such changes include an increase in infiltrating cytotoxic CD8+ T lymphocytes and antigen-presenting myeloid cells and a decrease in immunosuppressive Foxp3+ regulatory T cells. In addition, an increase in circulating ketone bodies elicited by fasting or a fasting-mimicking diet participates in degradation of the NRLP3 inflammasome, an effect that can be replicated by the activation of autophagy. Together these strategies limit inflammatory reactions and enhance the adaptive immune response to tumor cells.

context of cisplatin-based chemotherapy[62]. Moreover, high expression of pyridoxine kinase, the enzyme that converts pyridoxine into PLP, is associated with favorable prognosis in non-small-cell lung cancer[63]. High concentrations of 25-hydroxyvitamin D in serum are associated with favorable prognosis in patients diagnosed with breast cancer[64], prostate cancer[65] or colorectal cancer[66]. High concentrations of 25-hydroxyvitamin D in plasma are also correlated with a decreased frequency of colorectal cancers with little lymphocyte infiltration, which are associated with a particularly poor prognosis[67]. Furthermore, elevated concentrations of 25-hydroxyvitamin D in plasma are correlated with decreased proinflammatory markers and favorable prognosis in people with prostate cancer[68,69]. These results are reminiscent of those obtained for another well-established cancer-preventive agent, aspirin, which also decreases the incidence of colorectal cancers with low frequencies of tumor-infiltrating lymphocytes[70]. Moreover, these findings are similar to those of mouse experiments showing that knockout of the gene encoding the vitamin D receptor precludes the maturation and proliferation of intestinal CD8αα+ intraepithelial lymphocytes[71] and accelerates the development of colorectal carcinoma in cancer-prone *Apc*[Min/+] mice[72]. Supplementation with 1,25-dihydroxyvitamin D3 plus calcium in healthy volunteers has been found to induce measurable expression of immune-system-related genes in rectosigmoid colonic mucosa. Together, these findings support the idea that specific micronutrients stimulate anticancer immunosurveillance[73] (**Fig. 4**).

In addition to fiber, multiple distinct phytochemicals have been found to prevent colon-cancer development in mouse models, in a manner associated with effects on the gut microbiome and anti-inflammatory effects[10]. Serum concentrations of enterolactone, which reflect the uptake of dietary lignans, positively correlate with overall survival in women with postmenopausal breast cancer[74], and flaxseed lignin administered to postmenopausal women decreases the concentration of C-reactive protein[75]. The uptake of dietary spermidine, which is particularly abundant in some fruits, soybean sprouts and mature cheeses, has also been linked to an overall decrease in human cancer mortality[76]. In mice, spermidine supplementation decreases subclinical inflammation[76] and stimulates anticancer immune responses[77].

Coffee consumption has a prominent anti-inflammatory effect, as indicated by epidemiological studies linking the abundance of caffeine metabolites in the blood to the expression of inflammasome-related genes, the amounts of NLRC4-inflammasome-activating metabolites, such as adenine and N4-acetylcytidine and circulating IL-1β (ref. 78). Indeed, caffeine inhibits the secretion of IL-1β induced by adenine and N4-acetylcytidine[78]. Independently of its caffeine content, coffee also induces autophagy *in vivo*, in mice[79]. Whereas coffee consumption causes a dose-dependent decrease in overall and cardiovascular mortality, it does not affect cancer mortality, with the notable exception of hepatocellular carcinoma[80] and perhaps colorectal cancer[10,81].
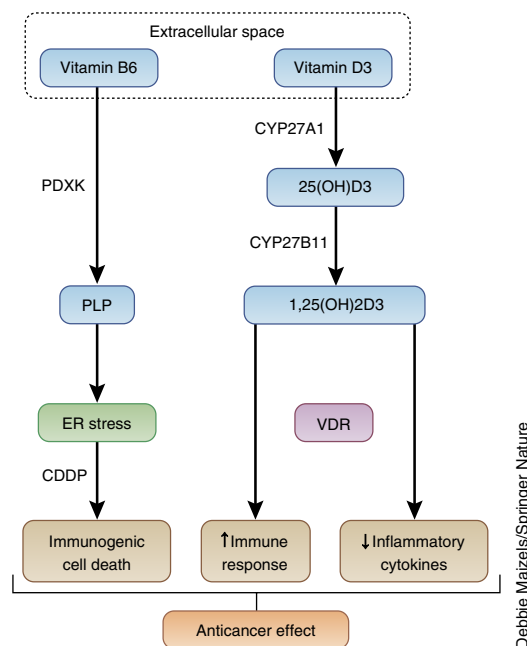
The consumption of nuts is also inversely associated with death due to cancer or cardiovascular disease[82,83]. Indeed, nut intake is associated with a diminished subclinical inflammatory status, as reflected by the plasma concentrations of C-reactive protein[83]. This effect might be related to the high content of omega-3 fatty acids in nuts, which are known for their health-promoting and anti-inflammatory effects[84], although this possibility requires further in-depth investigation.

The mechanisms that account for the main protumorigenic effects of red-meat consumption on cancer risk in multiple organs, such as the colon, prostate and breast, remain to be resolved[81]. One intriguing but unproven hypothesis posits that incorporation of an alien metabolite, N-glucolylneuraminic acid, which is particularly abundant in beef, into the tissues of red-meat consumers might lead to the proinflammatory induction of xenoantigen-specific antibodies[81]. Collectively, there is abundant but fragmentary evidence relating nutrition to the development and progression of cancer. In several cases, these links causally involve immunomodulatory effects.

Nutritional interventions for cancer treatment

For many decades, nutritional interventions have been conceived mainly to treat the wasting syndrome cachexia in terminally ill cancer patients. Cachexia is often caused by proinflammatory factors, such as TNF and IL-6 produced by tumor cells, and changes in systemic metabolism; it is characterized by systemic immunosuppression that may be due to elevated glucocorticoid tonus[85]. Here we discuss nutritional interventions for the treatment of cancer in a curative setting rather than a palliative setting.

Bariatric surgery decreases cancer mortality[86]; this is at odds with the observation that lean, formerly obese mice, in contrast to mice that have never been obese, carry an epigenetic memory that causes accelerated growth of transplantable mammary carcinomas[87]. In mouse models bearing a series of distinct transplantable cancers, treatment with one or several fasting cycles (usually for 48 hours, thus causing a transient but drastic decrease of ~20% in body weight) diminishes tumor growth, especially if the treatment is combined with chemotherapy[88]. Notably, most of the beneficial effects of fasting require an intact cellular immune system, given that tumors implanted into nude

Figure 4 Immune-system-mediated anticancer effects of dietary vitamin B6 and vitamin D3. Diet-derived vitamin B6 and vitamin D3 are inactive in their natural form. After being passively transported into cells, these molecules are converted intracellularly into metabolites that are responsible for the consequent biological effects. Within tumor cells, pyridoxine kinase (PDXK)-mediated phosphorylation of vitamin B6 results in the generation of its metabolite, PLP. By increasing endoplasmic-reticulum (ER) stress, PLP elicits immunogenic-cell-death features in cancer cells and hence enhances the antineoplastic activity of cisplatin (CCDP) in an immune-system-dependent fashion. Vitamin D3 undergoes hydroxylation reactions mediated by the cytochrome p450 enzymes CYP27A1 and CYP27B1 and is converted into bioactive 1,25-dihydroxyvitamin D3 (1,25(OH)$_2$D3) in hepatic, renal and immune cells. Through binding to nuclear vitamin D receptor (VDR), 1,25(OH)$_2$D3 promotes an anti-inflammatory and immunostimulatory gene-expression signature responsible for its cancer-preventive action. 25(OH)D3, 25-hydroxyvitamin D3.

mice, which lack T lymphocytes, do not result in decreased tumor growth after treatment with anthracyclines or oxaliplatin together with starvation[89]. Instead of starvation, a hypocaloric diet can be used to boost chemotherapy-induced anticancer immunosurveillance, with an increase in circulating and tumor-infiltrating CD8+ T cells, local depletion of regulatory T cells and a surge in common lymphoid precursor cells in the bone marrow[89]. Such effects have been linked to the upregulation of autophagy and the downregulation of Nrf2 and HO-1, proteins involved in anti-inflammatory responses in cancer cells[77,89] (**Fig. 3**). In addition, a hypocaloric diet has been shown to promote the regeneration of insulin-secreting pancreatic beta cells and thus to correct diet-driven metabolic syndromes[90]. Given these insights, fasting or hypocaloric diets might also prevent cellular transformation by maintaining the stemness of tissue-specific progenitor cells[91].

Starvation causes a rapid decrease in protein acetylation both in mouse tissues[33,77] and in peripheral blood mononuclear cells from human volunteers[47]. Protein deacetylation is a potent stimulus of autophagy and can be artificially induced by a series of caloric-restriction mimetics, which can be grouped into three categories: (i) agents, such as hydroxycitrate, that decrease the synthesis of cytosolic acetyl coenzyme A; (ii) agents, such as spermidine, that inhibit acetyltransferases such as EP300; and (iii) agents, such as resveratrol, that activate

deacetylases such as sirtuin-1 (ref. 92). Such agents, many of which are part of a normal diet, induce autophagy without causing immunosuppression and can be used to stimulate anticancer immune responses elicited by chemotherapy. This effect requires the induction of autophagy in cancer cells; activates an increase in the extracellular release of ATP from stressed tumor cells *in vivo*; favors remodeling of the immune-cell infiltrate with an increased recruitment of dendritic-cell precursors, for which ATP is a chemotactic factor; and improves the CD8^{+} cell/Foxp3^{+} cell ratio[77]. Similarly to starvation, treatment with caloric-restriction mimetics decreases free concentrations of the insulin-like growth factor IGF1. Replenishing IGF1 blocks autophagy induced by caloric-restriction mimetics and abolishes their anticancer effects[77]. Hence, the immunostimulatory effects of starvation and caloric-restriction mimetics overlap in their modes of action (**Fig. 3**). Notably, rapamycin, another drug that induces autophagy and increases longevity in model organisms, cannot be considered a typical caloric-restriction mimetic, because it does not decrease acetylation of cytoplasmic proteins[33,92].

Although they vary in their anticancer effects, ketogenic diets might prolong survival in animal models and human studies, as suggested by meta analyses, primarily in brain neoplasia[93,94]. Mice with intracranial glioblastomas exhibit improved tumor-reactive innate and adaptive immune responses, including increased cytokine production and cytolysis of tumor cells by specific CD8^{+} T cells, after treatment with a ketogenic diet. This effect is coupled to a decrease in markers of T cell exhaustion, such as PD-1 and CTLA-4 (ref. 95). Similarly, a ketogenic diet inhibits lactate production by glycolytic tumors, an effect secondary to a decrease in circulating glucose concentrations, and thereby reduces lactate-mediated local immunosuppression, which in turn decreases the frequency of myeloid-derived suppressor cells and improves anticancer immune responses[96] (**Fig. 3**).

Given the epidemiological evidence discussed above, it appears plausible to attempt dietary interventions or to provide food supplements that increase the uptake of spermidine and vitamins B6 and D (**Fig. 4**), although clinical trials using vitamin E and beta carotene have been unsuccessful or even have been associated with increased cancer incidence[97]. Vitamin B3 (nicotinamide) has been found in a phase III clinical trial to significantly decrease the incidence of nonmelanoma skin cancers, but its mode of action has not been determined[98]. This effect might be part of the general antiaging effect of nicotinamide[99], and evaluation of its chemopreventive or therapeutic action might be extended to other malignancies. In the course of such trials, it will be important to assess immunological parameters that might prove to be useful biomarkers and yield heuristic insights.

Concluding remarks and outlook

The premises noted above allow several overarching conclusions to be drawn. First, there is compelling evidence that nutrition has considerable effects on the incidence and progression of cancer and responses to treatment. Second, a lifestyle characterized by caloric excess, sedentarism and a high-fat, high-sugar Western-style diet tends to promote carcinogenesis through diverse intertwined mechanisms that include, but are not limited to, increased inflammatory reactions; diminished immunosurveillance; and a considerable abundance of energy-rich metabolites (such as glucose, fatty acids or amino acids) or trophic factors (such as insulin, insulin-like growth factor and leptin) that might stimulate the multiplication of malignant cells. Corrective interventions regarding the quantity and quality of nutrition have the potential to prevent cancer or slow its progression. Moreover, targeted interventions with defined macro- and micronutrients can dampen procarcinogenic inflammation and stimulate anticancer immunosurveillance.

Unfortunately, most past cancer research has been based on the assumption that the growth of malignant cells *in vitro* or in immuno-deficient mice reflects *in vivo* physiology, and the effects of metabolic factors on cancer growth have usually been studied with this perspective. Future work will need to integrate the fundamental effects of an intact immune system on the evolution of tumors. Doing so would require the use of holistic experimental approaches in which the effects of nutrition on cancer are studied in fully immunocompetent mice with a 'humanized' microbiome. Moreover, future clinical trials in this area must incorporate sophisticated immunomonitoring approaches to yield interpretable results.

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