Tumour biology

Diet analysis suggests lipid imbalance slows cancer

Giulia Salvadori & Valter D. Longo

Understanding how diet affects tumour growth could lead to better treatments. Analysis in mice reveals that a low-calorie diet, but not a ketogenic diet, slows the growth of pancreatic cancer. This effect is mediated by lipid changes.

Various diets, such as those that periodically restrict calorie intake and thereby drive metabolic changes associated with fasting (periodic fasting-mimicking diets)[1], or ones that are low in carbohydrates and high in fat (ketogenic diets), are emerging as nutritional interventions that can delay cancer growth and perhaps boost the effect of anticancer drugs[1,2]. Whereas long-term calorie restriction is not feasible for people on most cancer therapies because it leads to weight loss and lean body mass[3], ketogenic diets and periodic fasting-mimicking diets are beginning to be tested in a series of clinical trials, and are particularly promising when used in combination with standard therapies[1,2,4–6]. Writing in *Nature*, Lien *et al.*[7] fill in some of the missing details about how diet affects cancer growth.

Animal studies provide evidence suggesting that various dietary interventions can be potent in combination with standard anticancer drugs[4]. But the results also underline the importance of both the relative levels of calories, proteins, fats and carbohydrates in a diet, and the duration and frequency of the diet's administration. What makes the implementation of certain diets in the clinic even more complex is that they can be highly effective in combination with one drug, but ineffective with another. Thus, understanding the molecular mechanisms that enable dietary interventions to result in toxicity to cancer cells, or to increase the effectiveness of standard drugs, is essential to the development of standard-of-care (treatments routinely recommended by clinicians) cancer therapies that include a dietary component.

Lien and colleagues' study contributes molecular insights (Fig. 1) into how the effectiveness of different diets in slowing the growth of various cancers depends on how the diets affect the lipids in the blood and tumour. The authors examined mice that had one of two types of cancer: pancreatic ductal adenocarcinoma or non-small-cell lung cancer. Lien *et al.* assessed the effect of a diet in which a 40% reduction in caloric consumption was achieved by lowering carbohydrate intake; they also evaluated the effects of a ketogenic diet consisting of a normal level of calories but made up of an intake of 90% fat, 9% protein and 1% carbohydrates. The authors found that the low-calorie diet reduced tumour growth in these models, but the ketogenic diet did not, even though both diets led to a similar decrease in blood-glucose levels. Glucose levels have been reported to be fundamental for the survival and growth of many types of cancer, leading to the targeting of glucose metabolism as an anticancer therapeutic approach[8].

A possible reason for just one of the diets having an effect on the tumour is that only the caloric-restriction diet reduced glucose availability for cells in the tumour. However, because dietary interventions alter the levels of many metabolite molecules, Lien *et al.* explored whether nutrients other than glucose influenced the anticancer effects of the caloric-restriction diet. The authors measured the availability of fatty-acid molecules in the plasma component of blood and in the tumours. As expected, a ketogenic diet resulted in high levels of many types of fatty acid, whereas caloric restriction was associated with low levels of these fatty acids, raising the possibility that certain fatty acids support tumour growth.

Lien and colleagues show that both diets reduced the activity of an enzyme called stearoyl-CoA desaturase (SCD), which helps to produce monounsaturated fatty acids (those with one carbon–carbon double bond) from saturated fatty acids (those that lack carbon–carbon double bonds). SCD is needed for cancer cells to proliferate in a lipid-depleted environment, as reported by the authors. However, only the caloric-restriction diet reduced the levels of monounsaturated fatty acids and affected the ratio of unsaturated to saturated fats, suggesting that an imbalance between

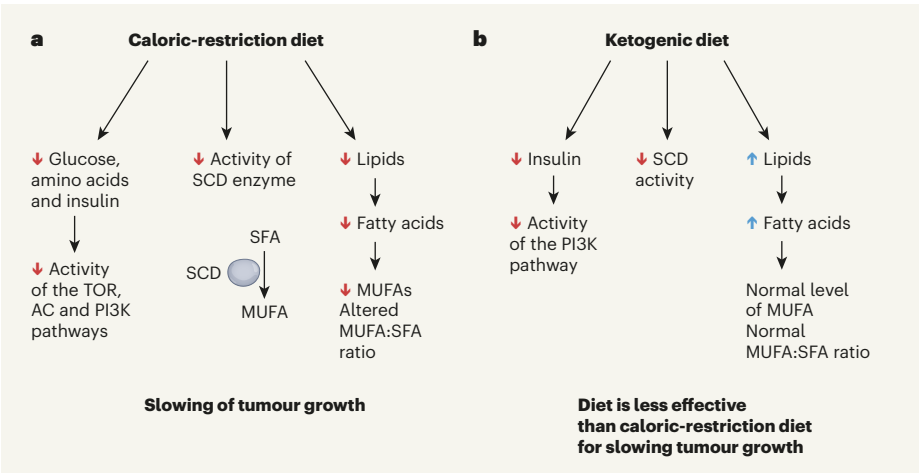

Figure 1 | How diet affects tumour growth in mice. a, A low-calorie diet slows tumour growth by lowering glucose, amino acids and the hormone insulin and thereby inhibiting various tumour-promoting signalling pathways (the TOR, AC and PI3K pathways)[4]. Lien *et al.*[7] report that this diet also inhibits the enzyme SCD, which can convert a saturated fatty acid (SFA) to a monounsaturated fatty acid (MUFA). The perturbed balance of fatty acids slows the growth of pancreatic tumours. **b**, A ketogenic diet, high in fat but of normal calorie content, also influences the insulin pathway as Lien *et al.* report. However, it does not alter the SFA:MUFA ratio, and it enables pancreatic tumours to grow.

these types of fatty acid affects tumour growth. The authors carried out experiments to test this hypothesis, and found that increasing the activity of SCD partially blocked the slowing of tumour growth caused by caloric restriction. When the authors examined the profile of fatty acids in SCD-expressing tumours, they observed a higher ratio of monounsaturated to saturated fatty acids than was evident in the mice on a caloric-restriction diet.

To test their proposed mechanism for how caloric restriction mediates the inhibition of pancreatic tumour growth, Lien *et al*. gave mice a high-fat, caloric-restricted diet rich in palm oil to restore the ratio of unsaturated to saturated fats back to that of mice on a normal diet. The authors report that this partially blocked the effect of caloric restriction on tumour growth. Notably, although the caloric-restriction diet was effective against pancreatic and lung cancer, the addition of palm oil stopped the diet's effects on tumour growth only in pancreatic cancer. This finding underlines the need to focus both on therapies targeted to specific cancers and on wide-acting dietary interventions that together have consistent antitumour effects. Indeed, long-term calorie restriction or the more-restrictive fasting mimicking diets (periodic cycles of a diet able to mimic the metabolic changes induced by water-only fasting) are effective against a wide range of cancers because they each reduce levels of several factors, including glucose and the proteins insulin, IGF-1, leptin and ferritin, moreover, they also alter the availability of amino acids and fats[9–11].

Although it is important to identify dietary changes that alone can delay tumour growth, it will be crucial to establish combinations of wide-acting dietary restrictions and targeted drugs that are highly effective against various cancers. Indeed, it was previously shown in mice[12] that cycles of fasting act similarly to the chemotherapy drug gemcitabine in delaying the growth of pancreatic tumours in mice, but that only the combination of fasting and gemcitabine had a strong effect in inhibiting the progression of pancreatic cancer.

Thus, Lien and colleagues' study sheds light on how low-calorie but not ketogenic diets can impair the growth of specific tumours, paving the way for further work aimed at evaluating the involvement of other metabolites in the survival of cancer cells.

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