NUTRITION

# Low-protein diet in cancer: ready for prime time?

*Roberto Pili and Luigi Fontana*

Diet has a recognized influence on cancer development and progression. However, the effect of diet modifications on the immune system remains elusive. Rubio-Patiño and colleagues provide evidence that a low-protein diet enhances the anticancer immune response in tumour-bearing mice, and highlight the potential of this diet intervention in patients with cancer.

*Refers to* Rubio-Patiño, C. et al. Low-protein diet induces IRE1α-dependent anticancer immunosurveillance. *Cell Metab.* **27**, 828–842.e7 (2018).

Numerous epidemiological studies have highlighted a link between diet and cancer risk[1,2]. Excessive consumption of calories and animal-derived proteins, reminiscent of a typical Western diet, yields an increase in circulating levels of insulin and free insulin-like growth factor 1 (IGF1)[1], which feed into the nutrient-sensing phosphatidylinositol 3-kinase (PI3K)–AKT (also known as PKB)–mammalian target of rapamycin (mTOR) pathway. Activating mTOR promotes macrophage-induced angiogenesis, whereas inhibiting mTOR promotes macrophage-mediated antitumour effect[3]. In contrast, consumption of large amounts of vegetables, legumes and fish is associated with reduced cancer incidence, progression and mortality[4]. Dietary protein restriction promotes health and longevity, and dietary amino acid restriction alters the gut microbiota, mTOR pathway activation, tissue repair, inflammation and immune tolerance[5,6]. However, it remains unclear how protein and amino acid restriction influences transcriptional activity and immune cell function in the tumour microenvironment where killer T effector cells (that is, $CD8^+$ T cells) control tumour development by so-called 'immunosurveillance', a defence mechanism through which immune cells can recognize and destroy malignant cells before they develop into tumours.

Rubio-Patiño and colleagues investigated the role of dietary protein restriction in modulating the immune response during tumour progression mouse cancer models[7]. Following the injection of lymphoma cells, the researchers fed mice isocaloric diets containing either 25% less protein or 25% less carbohydrates compared with a control diet, and observed that only the low-protein diet increased mouse survival by decreasing tumour growth. Interestingly, this observation was associated with an increase in IFNγ expression, a key cytokine for both innate and adaptive immunity, in the lymph nodes of lymphoma-bearing mice compared with mice fed a control diet. $CD8^+$ T cells or killer T cells are a subset of T lymphocytes capable of killing tumour cells. Mice fed the low-protein diet were associated with increased tumour-infiltrating $CD8^+$ T cells compared with mice fed a normal diet. Depleting $CD8^+$ T cells in immunocompetent mice did not improve mouse survival induced by the low-protein diet, suggesting a substantial involvement of these immune cells. Depletion of phagocytic cells (such as macrophages), which also contribute to immunosurveillance with $CD8^+$ T cells, abolished the low-protein-diet-mediated tumour control. Thus, reducing dietary protein intake can induce an antitumour immune response that involves tumour-infiltrating $CD8^+$ T cells.

The unfolded protein response pathways were upregulated in the tumour cells from mice fed the low-protein diet compared with tumour cells from mice fed the control diet. Interestingly, the researchers observed that inhibition of endoplasmic reticulum stress-dependent inositol-requiring protein 1α (IRE1α) and retinoic acid-inducible gene 1 protein (RIG1; also known as DDX58) signalling negatively impacted the anticancer immune response caused by the low-protein diet. This upregulation of IRE1α and RIG1 in tumour cells suggests that it might be the molecular mechanism underlying the tumour immune response induced by this dietary intervention. The researchers concluded that their data challenge the 'common dogma' that lowering protein in the diet limits tumour development by decreasing tumour proliferation and argue against a role of circulating IGF1 (even though this growth factor was not directly measured). They also propose that a low-protein diet induces a tumour cell IRE1α-dependent activation of anticancer-specific $CD8^+$ T cells that does not involve the mTOR pathway.

We have previously reported that an isocaloric diet with greater protein restriction (~65% less protein) than the low-protein diet utilized by the researchers had a substantial antitumour effect in human prostate and breast cancer models[8]. The dramatic inhibition of tumour growth was associated with a substantial inhibition of the nutrient-sensing mTOR pathway and abrogation of tumour cell proliferation. However, our findings were different from those observed by Rubio-Patiño and colleagues, who did not report a substantial modulation of the mTOR–AKT pathway. Interestingly, the decrease in tumour size induced by the low-protein diet was observed in immune-deficient mice that lack $CD8^+$ T cells, suggesting a direct antiproliferative effect on the tumour cells and/or an effect on the innate immune system[8]. Thus, compelling evidence now exists that dietary protein restriction has a potential anticancer effect, and either the antiproliferative or pro-immune response activity might be directly related to the level of protein restriction[7,8] (FIG. 1). Nevertheless, the common notion that a high-protein diet is beneficial in patients with cancer needs to be considered with caution.

An important question that remains pertains to the suitable level of dietary protein restriction to elicit the optimal antitumour immune response. Of note, the researchers found that a 12.5% and 25% reduction in dietary protein had a similar anticancer effect, but a 40% reduction didn't have any effect, suggesting not only the lack of a linear beneficial effect with this specific dietary restriction, but also a potential bimodal result[7]. This observation

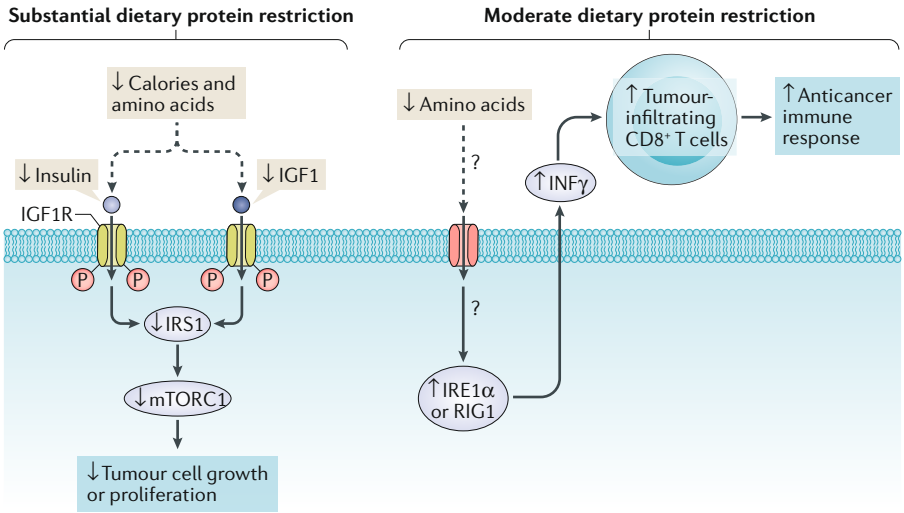


Fig. 1 | **Potential effects of different levels of dietary protein restriction.** A substantial protein and calorie restriction may directly inhibit tumour cell proliferation via the insulin–insulin-like growth factor 1 (IGF1)–insulin receptor substrate 1 (IRS1)–mammalian target of rapamycin complex 1 (mTORC1) axis. A moderate protein restriction may induce inositol-requiring protein 1α (IRE1α)–retinoic acid-inducible gene 1 protein (RIG1) expression in tumour cells, increase IFNγ secretion and subsequent recruitment of tumour-infiltrating $CD8^+$ T cells and induction of anticancer response. ? and dashed arrows represent unknown receptor and mechanism. IGFR1, IGF1 receptor.

might have translational importance and suggests the need to identify the 'sweet spot' for each patient or tumour type. In addition, the timing of the intervention might influence the effect of dietary protein restriction. The anticancer immune response might be different depending on when the intervention is implemented, for example, at the time of tumour initiation, when the disease is already established, or at the advanced stage. Furthermore, the amino acid composition and the different sources of food might be important to elicit the beneficial effect of dietary protein restriction. Intriguing data from our group indeed suggest that the anticancer effect achieved with dietary protein restriction might also be obtained by substituting animal-based protein casein with plant-based soy[8].

Overall, the data presented by the researchers provide quite compelling evidence for the potential role of moderate protein restriction on tumour progression, but not necessarily on tumour initiation. The low-protein diet was not tested in an oncogene-induced cancer model as reported with other dietary restriction interventions in order to study the early effects of immunomodulation on the establishment of a tumour[9]. In addition, the preclinical data from fasting-mimicking diets or caloric restriction on tumour immunosurveillance and immunoresponse suggest that different dietary restriction interventions might achieve similar results[9,10]. Transient dietary interventions in patients with cancer may be feasible but the most important question is whether these treatments will enhance the effect of the current and future immunotherapies. A more comprehensive understanding of the influence of low-protein diets and other dietary restrictions on the crosstalk between the innate and adaptive immune response will lead to a rationale for clinical testing.

It remains to be seen how, but not whether, these intriguing findings will be transferred into the clinic. Further studies are needed to characterize the specific role of modulating nutrient-sensing pathways on the different components of the tumour microenvironment. Even if the low-protein diet is not ready for 'prime time' yet, undoubtedly the work by Rubio-Patiño and colleagues seems to challenge a common belief that has been afflicting many patients with cancer — "does sugar feed cancer?" — and provide a rationale for a dietary lifestyle that might help them fight their disease.

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**Competing interests**
The authors declare no competing interests.