Published in final edited form as:

Nature. 2009 April 9; 458(7239): 713. doi:10.1038/458713a.

CANCER: When restriction is good

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Abstract

Dietary restriction can prolong life and delay the onset of cancer. Suppressing the signalling pathway that is mediated by the hormone insulin might be crucial for the anticancer effects of reduced caloric intake.

It is well established that dietary restriction, which involves limiting nutrient intake below normal levels but without reaching malnutrition, extends lifespan in most, if not all, species — probably including humans¹. This amazing benefit is likely to be due to the evolutionary advantage of keeping alive under suboptimal nutrient availability, and postponing reproduction until food is plentiful. On the basis of this evolutionary hypothesis, dietary restriction should prolong not only lifespan, but also youthfulness. Indeed, in both rodents and humans, limiting caloric intake delays many age-associated traits and diseases, including cognitive deterioration and cancer^{2,3}. But dietary restriction does not affect all types of cancer similarly⁴, raising questions about the generality of its effects and its mode of action in cancer. Writing in this issue, Kalaany and Sabatini⁵ (page 725) address these questions in both human tumour cells and animal models of human cancer.

The authors find that, when human-tumour cell lines are implanted into mice, some lines cannot expand if the animals' caloric intake is reduced by 40% for a period of 3 weeks. Intriguingly, the cell lines that were resistant to the antitumour benefits of this nutrient restriction carried mutations that led to the constitutive (continuous) activation of the signalling pathway mediated by the hormone insulin. Specifically, these cell lines had mutations that activated the enzyme PI3K, a key component of the insulin signalling pathway, or inactivated PTEN phosphatase, an enzyme that counteracts PI3K action. So it seems that, to exert its anticancer benefits, limited dietary intake must reduce insulin-mediated signalling.

To investigate whether reducing the activity of the insulin/PI3K pathway was indeed required for mediating the effects of dietary restriction, Kalaany and Sabatini next studied the consequences of short-term limitations in food intake on mice that had been genetically engineered to develop tumours with either a constitutively active PI3K pathway or constitutive activation of other oncogenic signalling pathways. Strikingly, only tumours with an active PI3K pathway were resistant to dietary restriction. What's more, activating this pathway was both necessary and sufficient for tumour resistance to reduced food intake. Finally, the FOXO proteins, which are major downstream targets of the PI3K signalling pathway and affect gene transcription, seem to execute the effects of dietary restriction, as FOXO transcription factors were inactivated in the tumours resistant to reduced nutrient intake (Fig. 1).

In search of a cellular mechanism to explain the effect of dietary restriction on tumours, Kalaany and Sabatini found that, in these tumour cells, there was an increase in programmed cell death (apoptosis). Further studies on how dietary restriction reduces tumour growth *in vivo* will be needed to explain whether it acts solely on the tumour itself, on the tumour microenvironment, or on both. Indeed, reduced food intake could affect other cellular processes

that contribute to tumour size. For instance, it might inhibit cell proliferation; it could trigger autophagy, a 'self-eating' cellular process that would help to recycle nutrients and ward off cancer by eliminating damaged proteins or organelles; or it might help to reduce the growth of new blood vessels in tumours — a process known as angiogenesis — thus affecting the tumour microenvironment rather than the tumour cells.

It would be informative to compare Kalaany and Sabatini's data⁵ with previous observations on the mechanisms of dietary-restriction-induced longevity and tumour suppression in other species⁶. Studies in yeast and worms have revealed various signalling pathways that mediate the effects of reduced food intake on longevity — including those involving the Sir2 family of deacetylase enzymes^{7,8}, the FOXA/*pha-4* (ref. 9) and NRF2/*skn-1* (ref. 10) transcription factors, and the AMPK (ref. 11), TOR (ref. 12) and Rheb (ref. 13) signalling molecules. Curiously, the insulin–PI3K–FOXO pathway was not essential for the effect of dietary restriction on longevity in most, although not all 11/13, of the studies. So how can these findings be reconciled with those of Kalaany and Sabatini?

There could be several explanations. First, compared with invertebrates, mammals may be more dependent on normal insulin signalling to extract maximum benefit from dietary restriction in relation to longevity and tumour resistance. Indeed, mutation of the growth-hormone receptor, which affects the production of insulin-like growth factor, interferes with dietary-restriction-induced longevity in mice¹⁴. Second, reduced insulin-mediated signalling resulting from a decrease in food intake may be even more important for fighting off cancer than for extending lifespan. In mice, for example, NRF2/*skn-1* mediates the effects of dietary restriction on cancer but not on longevity¹⁵. Third, the methods that researchers use to restrict dietary intake in invertebrates may expose pathways other than that mediated by insulin. Reduced food intake probably engages several pathways that cooperate to prolong lifespan and prevent cancer. Understanding how these pathways regulate longevity and age-dependent traits will be crucial for harnessing the full benefits of nutrient restriction.

It is worth noting that Kalaany and Sabatini implemented reduced food intake for a short period (3 weeks), whereas it is known that longer restriction regimens (several months to years) are needed to extend lifespan¹. It would be informative to know whether longer dietary-restriction regimens can still suppress tumours, or if tumours recur after a while. Could responsive tumours become resistant to the beneficial effects of dietary restriction with time, just as they acquire resistance to chemotherapy? This, in turn, raises the possibility that downregulation of insulin-mediated signalling through reduced food intake may only initiate the anti-cancer benefits; other pathways might need to be activated to maintain its suppressive effects on tumours. Finally, in mammals and other species, different dietary-restriction regimens can all extend lifespan. It would be interesting to test whether different regimens could also reduce PI3K-dependent cancer expansion, as only some regimens might be realistically applicable to humans — for instance, feeding every other day rather than a 40% restriction every day.

As for cancer prevention and anticancer therapies, simply decreasing food intake might help to delay the onset of cancer. Moreover, involvement of the insulin-mediated pathway indicates that drugs that ameliorate insulin resistance in type 2 diabetes might be beneficial in preventing cancer, even in non-diabetic patients. One could also envisage using dietary restriction as a possible therapy in some specific cancers, and to predict which tumours would be vulnerable to such treatment on the basis of their mutation profiles, in particular in the genes encoding PTEN and PI3K. Limited food intake, together with a PI3K-pathway inhibitor, might have synergistic effects on cancer regression in tumours that have mutations in *PI3K* and/or *PTEN* genes. In addition, depriving tumours of nutrients locally by means of anti-angiogenic drugs, which would interfere with the tumour's blood supply, may be yet another way to apply the beneficial effects of dietary restriction. In general, developing such additional strategies to

mimic restriction could be particularly useful, because — as we all know — restricting food intake is notoriously difficult to implement in humans, and may even be psychologically damaging.

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Figure 1. Dietary restriction, insulin-mediated signalling, and cancer

Activation of cell-surface receptors by insulin triggers a signalling cascade in the cell that is mediated by the enzyme PI3K and subsequently by FOXO transcription factors. Kalaany and Sabatini⁵ find that dietary restriction reduces the activity of this pathway in some tumour cells, thereby enhancing cell death and reducing tumour size. However, tumours in which this pathway is constitutively active — owing to mutations in PI3K or in the PTEN enzyme, which normally counteracts PI3K — are resistant to the beneficial effects of dietary restriction.