Expert Opinion

Could starvation minimize chemotherapy-induced toxicities?

Evaluation of: Raffaghello L, Lee C, Safdie FM, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci USA 2008;105(24):8215-20

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Background: In their recent paper Raffaghello, *et al.* examined the use of short-term starvation (STS) to induce differential stress resistance (DSR), that is increased protection of normal over cancer cells against chemotherapy-induced oxidative stress, using a range of model organisms. *Objective/methods*: We examine the results of this study and their significance. *Results/conclusions*: Raffaghello, *et al.* obtained evidence that STS induced DSR in yeast, mammalian cell cultures, and mice. It is possible that calorie restriction extends lifespan and prevents chronic diseases like tumors, by braking proliferation. We think that molecular mechanisms determining STS-induced DFS in mammals should be thoroughly studied and clarified before starting to test this reasonable strategy in clinical trials.

Keywords: differential stress resistance, IGF1, starvation

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1. Introduction

Starvation, commonly defined as a prolonged deprivation of food, has been recently proposed by Raffaghello, *et al.* as a novel strategy to induce differential stress resistance (DSR), that is, increased protection of normal over cancer cells against chemotherapy-induced oxidative stress [1].

Tumor cells can proliferate in the absence of stimulatory growth signals, by the constitutive activation of one or more cancer-involved pathways, such as IGF1-R/Ras/Akt [2]. Calorie intake reduction as well as dietary restriction have been reported previously to downregulate the IGF1 signaling pathway and are associated with an increased stress resistance [3,4]. In yeast, the deletion of Saccharomyces protein kinase C homolog 9 (SCH9) and/or ras proto-oncogene homolog 2 (RAS2) genes, orthologs of components of the human IGF1-activated oncogenic pathway, mimic partially starvation-dependent resistance to oxidative stressors and cause proliferation blockage [5].

Most of chemotherapeutic agents are known to cause DNA damage and/or oxidative injury. Although these drugs should be much more toxic to cancerous than to normal cells, their selectivity is not complete, so that massive damage is delivered not only to tumor cells but also to normal tissues, especially with high-dose chemotherapy.

To test if a starvation-dependent DSR would be effective in protecting normal but not cancer cells against pro-oxidants/chemotherapeutics, the authors performed experiments in different models, such as yeast, mammalian cells and mice.

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2. Results from the paper

To investigate DSR against oxidants and genotoxins in yeast, the combination of starvation with the deletion or constitutive activation of SCH9 and/or RAS2 genes was tested. The authors found that short-term starvation (STS) in association with SCH9 and/or RAS2 deletion protected cells highly against H_2O_2 or the superoxide-generating agent menadione, compared with RAS2-expressing yeast cells. When a mixture of SCH9-lacking (normal-like) and RAS2-expressing (tumor-like) yeast cells at a 25:1 ratio was exposed to either cyclophosphamide and methylmethane sulphonate, a 1,000-fold differential toxicity between normal- and tumor-like cells, similar to that observed using oxidants, was reported.

In order to determine whether the DSR observed in yeast would also occur in mammalian cell lines as a result of STS obtained by glucose deprivation of the media, primary glial, glioma and glioblastoma cells were incubated with increasing concentrations of the above mentioned pro-oxidants and chemotherapeutic agents. The results confirmed that STS could induce different resistance between normal and neoplastic cells.

Finally, to verify if STS could protect against high-dose chemotherapy *in vivo*, the survival of prestarved mice was compared with that of unstarved controls after an unusually high dose of etoposide (80 – 110 mg/kg). Of the 28 prestarved mice only 1 died after treatment, while more than 50% of the 37 non-prestarved mice died of toxicity. When neuroblastoma cells were injected into mice to cause experimental metastases, which should cause death within 30 days, the survival of these mice was significantly longer with high-dose etoposide given after STS.

3. Significance of the results

In the paper by Raffaghello, *et al.*, the authors remarked that not only new drugs but also different strategies ameliorating the risk/benefit ratio of old drugs may offer new hopes for cancer patients.

In fact, since the era of targeted therapy started, in the late 1990s, much time, effort and money have been wasted in spasmodic research into biological markers associated specifically with carcinogenesis. Unfortunately, even when a target is found and blocked no prolonged inhibition of cancer cells proliferation can be obtained, due to the redundancy of proteins involved in cell-signaling networks.

The 'classic' cytotoxic agents exert antitumor action through killing cells that are actively proliferating preferentially, so injuring rapidly dividing cells, such as blood cells and the bowel epithelium.

Instead of keeping looking for the so-called 'needle in a haystack', researchers could focus their attention on protecting normal tissues from adverse effects of old drugs. A gain in drug resistance along with reduced toxicity could be consistent with the entry of most of the normally dividing cells, but not of the cancer cells, into a cell-cycle-arrested mode. The authors suggested that such a 'high protection' condition could be induced in response to STS and could allow the delivery of drug at doses much higher than those commonly used in clinical practice.

4. Expert opinion

Molecular interactions underlying growth and aging have been investigated extensively in yeast and worms and several homologous proteins that regulate longevity have been identified in IGF1-like pathways [6]. Common preserved growth pathways regulate both cell senescence and tumor transformation so that IGF1-receptor signaling is also involved highly in cancer development [7]. It might be possible that calorie restriction extends lifespan and prevents chronic diseases like tumors, by braking proliferation [8]. The same mechanism has been proposed to protect normal cells but not cancer cells whose proliferation is not dependent on growth signals, against the toxicity of chemotherapy drugs. The 40% decrease in circulating IGF1 levels, ascertained in mice after 36 h of starvation, raised the possibility that decreasing IGF1 signaling may be involved in the protective effect of starvation [9].

Probably the most relevant finding of the present study is that, when high doses of cytotoxic agents are administered to prestarved mice, no visible sign of acute toxicity is observed, while non-prestarved mice show significant toxicity and lose 20 – 30% of their weight following chemotherapy. In contrast, prestarved animals gain back the weight lost during the starvation period.

Experimental data supporting the potential efficacy and safety of multiple cycles of STS followed by high-dose chemotherapy are still lacking, so that more evidence on different types of cancers treated with various chemotherapeutic agents are required before clinical evaluation.

We think that molecular mechanisms determining STS-induced DFS in mammals should be thoroughly studied and clarified before starting to test this reasonable strategy in clinical trials.

Moreover the proposal to reduce dietary intake in cancer patients must be carefully evaluated. Tumor growth involves profound endocrine and metabolic alterations, which can lead to the onset of cancer anorexia–cachexia syndrome (CACS), especially when the disease is at an advanced stage. CACS is characterized by reduced food intake directly related to cancer and its treatment and is associated with muscle and fat wasting. Hypercaloric feeding has been proposed to reverse the depletion of lean body mass, even if metabolic adaptations, in particular the increase in protein catabolism, could limit the weight gain.

The intuitions by Raffaghello, *et al.* should promote new studies aimed at finding strategies for protecting normal cells against injuries determined by chemotherapy drugs.

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