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Review

Protective effects of short-term dietary restriction in surgical stress and chemotherapy

Sebastian Brandhorst^a, Eylul Harputlugil^b, James R. Mitchell^{b,**}, Valter D. Longo^{a,c,*}

^a Longevity Institute, School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA

^b Department of Genetics and Complex Diseases, Harvard T. H. Chan School of Public Health, Boston, MA 02115 USA

^c IFOM, FIRC Institute of Molecular Oncology, 20139 Milano, Italy

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ABSTRACT

Reduced caloric intake including fasting, as well as the dietary composition or the timing of food intake, impact longevity, likely through a modification in the onset or the severity of chronic aging-related diseases such as cancer. As with pre- and post-operative dietary recommendations, evidence-based nutritional advice from healthcare professionals during and after cancer treatment is often vague or conflicting. We hypothesize that preventive dietary recommendations can help in the context of both chronic cancer treatment efficacy and the avoidance of development of secondary malignancies, as well as in the context of protection from the acute stress of surgery. In this perspective review, we will discuss the latest findings on the potential role of short-term dietary restriction in cancer treatment and improvement of surgical outcome.

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* Corresponding author at: University of Southern California, Longevity Institute, School of Gerontology, and Department of Biological Sciences, 3715 McClintock Ave, 90089, Los Angeles, USA.

** Corresponding author at: Department of Genetics and Complex Diseases, Harvard T. H. Chan School of Public Health, 655 Huntington Ave. Building 2-121, Boston, MA 02115, USA.

E-mail addresses: jmitchel@hsph.harvard.edu (J.R. Mitchell), vlongo@usc.edu (V.D. Longo).

1. Introduction

The increasingly older population in most developed countries will likely experience one or more aging-related chronic diseases and conditions such as diabetes, metabolic syndrome, cardiovascular disease, osteoporosis, arthritis, dementia and/or cancer. Genetic and environmental factors, but also lifestyle choices including physical activity and dietary habits, play essential roles in disease onset, progression and treatment prognosis. For example, diet-related obesity is a well-established risk factor for multiple chronic aging-related diseases, including some of the most prominent cancers such as breast cancer in post-menopausal women, colorectal, hepatic, pancreatic or advanced prostate cancer (De Pergola and Silvestris, 2013). Prostate cancer, the second most common malignancy in men, has an approximately six-fold higher incidence in Western than in non-Western countries, most likely due to differences in dietary patterns (Kolonel et al., 2004). Obesity is also associated with a poor prognostic outcome, higher risk for cancer recurrence, comorbidity and disease-specific or overall mortality (Demark-Wahnefried et al., 2012).

Evidence that mammalian longevity can be prolonged by reducing total food consumption emerged during the early 1900s (Moreschi, 1909), but it was not until the 1990s that reduced food intake without malnutrition became extensively used in experimental models as a means to delay the aging process itself (Longo and Mattson, 2014). Today, a plethora of studies in model organisms has demonstrated that modifications in calorie intake, dietary composition (e.g. protein content), or timing of food intake (e.g. intermittent fasting), collectively referred to here as dietary restriction (DR), can have a major impact on longevity, likely through a delay in onset and reduction in severity of chronic aging-related diseases including cancer (Fontana and Partridge, 2015; Longo and Panda, 2016).

In addition to preventing or treating chronic disorders, DR can also increase resistance to a variety of acute stressors, ranging from heat shock to oxidative stress, across evolutionary boundaries (Fontana et al., 2010). In rodent models, one of the acute stressors against which various DR regimens protect is the clinically relevant stress of major surgery, which occurs with increasing regularity in elderly populations (Mitchell et al., 2013; Mitchell et al., 2009). As with chronic diseases of aging, genetic and environmental risk factors including obesity not only predispose individuals to the need for surgical interventions, for example cardiovascular surgery to address occluded blood vessels, but also increase the risk of surgical complications, including heart attack or stroke (Poirier et al., 2006).

As with pre- and post-operative dietary recommendations, evidence-based nutritional advice from healthcare professionals during and after cancer treatment is often vague or conflicting. Here we provide a perspective on how preventive dietary recommendations could help in the context of both chronic cancer treatment efficacy and the avoidance of development of secondary malignancies, as well as in the context of protection from the acute stress of surgery. In this review, we will discuss the latest findings on the potential role of short-term dietary restriction in cancer prevention and improvement of surgical outcome.

2. Nutrient sensing signaling pathways in dietary restriction-mediated longevity and stress resistance

In mammals, various forms of partial or complete food deprivation, here referred to generally as dietary restriction (DR), have been investigated, ranging from daily 20%–40% reduced calorie intake (calorie restriction, CR), restriction of specific nutrients without affecting daily calorie intake (e.g. protein restriction (PR) consist-

ing of low protein diets compensated with high fat; or restriction of sulfur amino acids, also known as methionine restriction, MR), intermittent fasting (IF, including alternate day fasting, ADF) and periodic fasting (PF). The benefits of DR on rodent lifespan have been extensively studied and are beyond the scope of this review. Generally, DR extends the lifespan of rodents and this extension is accompanied with a lower incidence of most chronic diseases and results in a more youthful metabolic state (Fontana et al., 2010; Mair and Dillin, 2008). CR, PR, MR, IF/ADF, and PF may all promote stress resistance and longevity in model organisms ranging from unicellular yeast to mammals, indicating that the underlying molecular mechanisms are at least partially conserved in many species (Fontana et al., 2010; Longo and Mattson, 2014; Robertson and Mitchell, 2013); although most likely with varying levels of efficacy.

IF is the most studied fasting method in rodents and has been demonstrated to promote protection against multiple diseases (Goodrick et al., 1990; Mattson, 2012; Mattson and Wan, 2005). The major difference between IF and PF in mice is the severity, including duration and/or frequency, of the fast. IF cycles usually last 24 h and are separated by one day of normal food intake (alternate day feeding), whereas PF cycles last 2 or more days and are at least 1 week apart to allow for regaining of normal weight (Longo and Mattson, 2014). Owing to this difference, the molecular changes of a variety of growth factors (including IGF-1) and metabolic markers (such as ketone bodies, serum glucose, etc.) differ significantly in their response (Longo and Mattson, 2014; Longo and Panda, 2016).

Recent studies indicate that both single bouts of fasting as well as PF have potent protective effects against many cytotoxic insults, ranging from chemotherapeutics to multifactorial surgical stress. For example, PF prior to lethal oxidative stress induced by etoposide protects from chemotoxicity and causes a significant increase in survival in five different mouse strains (Raffaghello et al., 2008; Tinkum et al., 2015). Similarly, 72 h of a water-only fast before treatment with doxorubicin protects CD-1 mice against oxidative stress-related cardiotoxicity (Lee et al., 2010). Fasting also has protective effects against the multi-factorial stress of ischemia reperfusion injury, including oxidative stress, in the mouse kidney and liver and rat brain (Mitchell et al., 2009; van Ginhoven et al., 2009; Varendi et al., 2014; Verweij et al., 2011). Fasting also ameliorates traumatic brain injury through neuro-protective effects, reduced oxidative damage and improved cognitive function (Davis et al., 2008).

Over the last 20 years, diet-based interventions have been combined with genetic approaches to identify the genes and pathways that mediate nutrient-dependent effects on longevity and healthspan. Sufficient nutrient supply enables organismal growth and proliferation, whereas periods of low food availability or the lack of specific macromolecules activate protective metabolic pathways to ameliorate the accumulation of cellular damage and to ensure reproductive fitness (Harrison and Archer, 1989; Madia et al., 2009). Notably, the response to these opposing environmental conditions is regulated by overlapping pathways: nutrient abundance, resulting in the activation of nutrient-sensing signaling cascades, promotes cellular growth while nutrient scarcity down-regulates these signaling pathways, thereby blocking cellular proliferation and activating stress resistance transcription factors which negatively regulate pro-aging pathways (Fontana et al., 2010; Guarente and Kenyon, 2000; Kenyon, 2001; Longo, 1999; Longo and Finch, 2003). Evolutionary conserved orthologues of the genes that regulate lifespan and stress resistance in lower eukaryotes, including *S. cerevisiae* and *C. elegans*, also regulate stress resistance and/or lifespan in mammals (Bonkowski et al., 2009; Brown-Borg, 2009; Coschigano et al., 2003; Holzenberger et al., 2003; Selman et al., 2009).

In laboratory mice, mutations in the insulin/growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis increase lifespan by up to 150% (Brown-Borg et al., 1996; Murakami, 2006). Cells derived from long-lived mice with deficiencies in the GH/IGF-1 axis have higher resistance against H₂O₂ induced oxidative stress, UV, genotoxins, and other stressors including heat and cadmium (Murakami, 2006; Salmon et al., 2005); in agreement with the findings in lower eukaryotes. Mice that over-express GH have a shorter lifespan compared to wildtype control and have decreased activities of the anti-oxidant enzymes superoxide dismutase and catalase (Bartke et al., 2002; Brown-Borg and Rakoczy, 2000; Brown-Borg et al., 2002). Finally, long-lived GHRKO mice subject to DR don't gain further benefits with respect to improved insulin sensitivity or lifespan, suggesting an overlapping, epistatic relationship between GH/IGF-1 signaling and DR-dependent nutrient sensing pathways (Bonkowski et al. 2009). Finally, it is important to note that not all genetic backgrounds experience a lifespan extension and some can even display reduced longevity under 40% CR conditions, indicating genetic variability in the response to CR (Liao et al., 2010; Sohal and Forster, 2014). In a recent study, Mitchell and colleagues provided further evidence that multiple factors, including mitochondrial ultrastructure and function, alter the response to CR. However, while the effect of CR on health is consistent across strains and sexes, survival is not correlated with CR in all cases (Mitchell et al., 2016). This is likely due to tradeoffs between effects on aging and effects on systems which may benefit from a higher calorie intake and/or fat level (Rikke et al., 2010). CR is more likely to extend lifespan in strains of mice with the lowest reduction in fat under CR (Liao et al., 2011). Notably, long-lived strains, including the Ames and Snell dwarf mice, display high percentages of body fat despite being smaller than their littermates. In humans, work has shown that being slightly overweight is associated with the lowest level of all-cause mortality (Flegal et al., 2013; Grabowski and Ellis, 2001).

3. Fasting in cancer treatment

Tumor cells arise from pre-cancerous cells through changes in the environmental niche, and the combination of cellular damage and DNA mutations over time (Hanahan and Weinberg, 2011), thus making aging the major risk factor for the development of many cancers (Campisi et al., 2011; DePinho, 2000). Notably, studies that focus on organismal aging also emphasize the preventive role of many dietary interventions in cancer establishment. Moreschi and colleagues demonstrated over a century ago the first direct relationship between chronic CR and the prevention of tumor transplantation in mice (Moreschi, 1909). Following this milestone, a multitude of studies has established that CR reduces the incidence and progression of spontaneous or induced tumors in various animal models including rodents and primates (Berrigan et al., 2002; Colman et al., 2014; Hursting et al., 1994; Mattison et al., 2012; Tannenbaum, 1940, 1996; Weindruch and Walford, 1982; Weindruch et al., 1986). In a multitude of auto- and xenograft mouse tumor models, CR causes potent anti-growth effects, although resistance has been observed in some cells with mutations that cause a constitutive activation of the phosphatidylinositol-3-kinase (PI3K) pathway (Kalaany and Sabatini, 2009). Support for the potential application of CR in humans arose from a 20-year longitudinal adult-onset 30% CR study in rhesus monkeys at the Wisconsin National Primate Research Center which decreased cancer incidence by 50% (Colman et al., 2009) and a 23-year study in rhesus macaques conducted at the National Institute on Aging (NIA) where neoplasia was identified in 5 of the 6 control monkeys but not in young-onset CR monkeys (Mattison et al., 2012). The incidence was similar between the control and old-onset CR groups indicat-

ing that early intervention may be necessary to have an impact on cancer (Mattison et al., 2012).

If CR may reduce cancer incidence in humans remains largely unknown, although CR, when combined with protein restriction (Fontana et al., 2008), can reduce clinical markers associated with cancer (Longo and Fontana, 2010). The large amount of data indicating benefits in cancer prevention in most animal models also supports the idea that CR could potentially be utilized as a means to delay cancer recurrence for patients in which cancer has been successfully removed; however currently no clinical trials have been carried out that demonstrated this. The use of CR as an acute therapy or preventive intervention remains problematic because chronically restricting the calorie intake of cancer patients would be extremely difficult to include into existing prevention or treatment paradigms, even if a benefit was demonstrated. Also, as a treatment option chronic CR merely delays the progression of an already established disease (Bonorden et al., 2009; Mukherjee et al., 2004), and its effectiveness might be reduced in a subset of CR-responsive cancers (Kalaany and Sabatini, 2009). In addition, chronic CR may simply be not feasible for cancer patients receiving chemotherapy, surgery or immunity-based treatments, or who are at risk for losing weight and becoming frail and cachectic because CR is generally associated with weight loss (Fontana et al., 2010; Kim and Demetri, 1996; Kristan, 2008; Reed et al., 1996). Periodic fasting induces metabolic changes which delay the incidence and growth of cancer cells, without the limitations of chronic CR. PF decreases blood glucose in mice by up to 75% whereas long-term CR or IF cause only a moderate 15% reduction (Lee and Longo, 2011; Longo and Mattson, 2014), a notable effect when considering the glucose dependence of many malignant cells (Vander Heiden et al., 2009; Warburg, 1956). PF reduces the pro-proliferative growth-factor IGF-1 by up to 75% (Lee et al., 2010; Underwood et al., 1994), while chronic CR causes a 25% IGF-1 reduction in mice (Barger et al., 2008) and only causes a 30% reduction in IGF-1 for humans when chronic DR is combined with protein restriction (Fontana et al., 2008).

Fasting for 8 days, or 40% CR for 3 months, reduces pre-neoplastic liver masses by 20–30%, lowers DNA replication but increases apoptosis and thus reduced the number and volume of putative pre-neoplastic liver foci by 85% throughout the following 17 months in rats (Grasl-Kraupp et al., 1994). Of note is however that the refeeding phase following a fast is associated with increased cellular proliferation in the liver and colorectal epithelium (Brandhorst et al., 2015; Cuervo et al., 2005) and thus exposure to carcinogens during this period enhances the growth of aberrant crypt foci in the colorectal mucosa and mammary tumors even by otherwise non-initiating carcinogen doses (Premoselli et al., 1998; Sesca et al., 1998; Tessitore et al., 1999), in contrast to the protective effect of chronic CR on carcinogenesis (Tagliaferro et al., 1996). It is therefore of importance that food intake after any PF cycle should be initiated only after elimination of the carcinogenic chemotherapeutic from the body.

3.1. Fasting induced differential stress resistance

The constitutive activation of pro-proliferative pathways plays a central role in promoting cancer growth and survival. As such, Ras and Akt function in signal transduction pathways that are frequently constitutively activated in many cancerous cells (Hanahan and Weinberg, 2000; Kinzler and Vogelstein, 1996; Medema and Bos, 1993). PF inactivates these evolutionary conserved nutrient-sensing signaling cascades and thereby also induces the resistance to oxidative and other stresses. This interconnection of cellular proliferation and stress resistance provides the foundation for a fasting-induced differential protection of normal cells from toxicity induced by most chemotherapeutic agents. The differential stress resistance (DSR) hypothesis is based on the fact that in

response to nutrient-scarce environmental conditions such as fasting, normal cells drastically reduce the number of cell divisions, utilize metabolites generated from the breakdown of fats, proteins and organelles, and become highly stress-resistant (Longo et al., 1997; Raffaghello et al., 2008). Cancer cells on the other hand are unable to enter a non-dividing and protected state due to the acquired self-sufficiency in growth signaling through gain-of-function mutations in oncogenes (e.g. Ras, Akt, mTOR) that constitutively activate proliferation pathways, and their ability to disregard anti-proliferative signals, such as those occurring during fasting, through loss-of-function mutations in tumor-suppressor genes (e.g. Rb, p53, PTEN) (Hanahan and Weinberg, 2000). DSR therefore presents a dietary intervention that increases the cellular resistance against cytotoxic chemotherapy or other drugs through detoxification systems in normal cells without affecting the efficacy of these agents against malignant cells (Raffaghello et al., 2008). The fasting-induced protection against otherwise lethal doses of the chemotherapeutic drugs has been demonstrated *in vivo*: fasting protects various mouse strains from high-dose etoposide toxicity (Raffaghello et al., 2008; Tinkum et al., 2015), protects CD-1 mice from high-dose doxorubicin (Lee et al., 2010), and protects Fabp1Cre;Apc^{15lox/+} mice against irinotecan induced weight loss, reduced activity, ruffled coat, hunched-back posture, diarrhea, and leukopenia (Huisman et al., 2015). Fasting reduces the delayed-type chemotherapy-induced nausea and vomiting in cancer-bearing dogs receiving doxorubicin (Withers et al., 2014). Analogously, the conditional liver-specific igf-1 gene deletion (LID) in transgenic mice, which results in a 70–80% reduction in circulating IGF-1 levels, results in the protection against cytotoxic chemotherapy drugs such as cyclophosphamide, doxorubicin and fluorouracil (Lee et al., 2010). Restoring IGF-1 to normal levels during fasting reverses the protection against lethal doses of doxorubicin (Lee et al., 2010). The protective effect of fasting is at least in part mediated by changes to the stem cell population. Fasting before high dose etoposide treatment preserves the architecture and barrier function of the small intestine by maintaining the viability of *Lgr5*, *Bmi1* or *HopX* expressing crypt stem cells (Tinkum et al., 2015). PF reduces the immunosuppression and mortality of the chemotherapeutic drug cyclophosphamide through changes in the signal transduction pathways of long-term hematopoietic stem cells and niche cells to promote self-renewal and lineage-balanced regeneration (Cheng et al., 2014), in agreement with preliminary findings on the PF-induced protection of lymphocytes from chemotoxicity in cancer patients (Safdie et al., 2009). PF also promotes regenerative effects in the blood, liver, muscle and nervous system, indicating that fasting stimulates the regeneration of healthy cells and tissue following tissue damage after chemotherapy (Brandhorst et al., 2015; Cheng et al., 2014).

3.2. Fasting induced differential stress sensitization

Cancer cells develop in a highly nourished environment, and the reduced availability of glucose and amino acids during fasting presents a significant disadvantage to tumor cells that usually experience an almost unlimited nutrient supply. Malignant cells rely on glycolysis more than on oxidative phosphorylation (Warburg effect), to provide them with energy and biosynthetic precursors essential for proliferation, and thus favor high levels of glucose (Vander Heiden et al., 2009). The Warburg effect allows for tumor cell survival and apoptosis evasion through decreased respiration and the restriction of cytochrome c-induced apoptosis (Ruckenstuhl et al., 2009; Vaughn and Deshmukh, 2008). Notably, glucose metabolism alone does not supply all the required building blocks necessary for cell-proliferation and cancer cells therefore depend on the availability of amino acids, particularly glutamine, as a nitrogen source (Vander Heiden et al., 2009). In line with

this requirement of cancer cells, protein/amino acid restriction have been demonstrated to delay the onset of many aging-related diseases, including cancer, and increase longevity (Mirzaei et al., 2014).

The same mutations that allow the unrestricted proliferation of tumor cells in a nutrient-rich environment also sensitize cells to alterations in the cellular environment. The mutations that accumulate in cancerous cells can be viewed as mostly detrimental given that gain-of/loss-of-function mutations likely restrict the response to any condition that is not ideal for the cancer cell. For example, a mutation that requires high levels of glutamine would not be deleterious until glutamine becomes restricted. In *S. cerevisiae*, oncogene-like RAS2val19 expression reverses the water-starvation induced protection against menadione and hydrogen peroxide, and sensitizes yeast cells to both cytotoxic stressors when compared to wild-type cells, a phenomenon termed Differential Stress Sensitization (DSS) (Lee et al., 2012).

In vitro models of PF by reducing glucose and/or serum availability in the growth medium sensitizes 15 of 17 human and rodent cancer cells lines to the chemotherapeutic agents doxorubicin and/or cyclophosphamide (Lee et al., 2012). Similarly, fasting sensitizes mouse, rat and human glioblastoma multiforme cells, but not primary mixed glia, to treatment with the chemotherapy drug temozolomide (Safdie et al., 2012). For human mesothelioma and lung carcinoma cells, serum starvation alone is sufficient to induce sensitization to cisplatin (Shi et al., 2012). In subcutaneous models of melanoma and breast cancer *in vivo*, PF cycles are as effective as chemotherapy alone whereas the combination of both treatments greatly improves treatment efficacy (Lee et al., 2012). In a metastatic mouse neuroblastoma model, fasting followed by the single administration of a high-dose chemotherapy cocktail containing doxorubicin and cisplatin successfully reduces drug toxicity and metastases and results in long-term cancer-free survival (Lee et al., 2012). PF prior to gemcitabine injection significantly decreases pancreatic tumor progression by more than 40%, in part through the increased uptake of gemcitabine (D'Aronzo et al., 2015). Cisplatin in combination with PF reduces mesothelioma progression by more than 60% compared to the control and a complete remission is observed in 60% of the mice treated with PF/cisplatin (Shi et al., 2012). 48 h of water-only fasting sensitizes intracranial and subcutaneous glioma models to radio- and chemotherapy (Safdie et al., 2012), an effect not observed by dietary protein restriction alone (Brandhorst et al., 2013). PF alone or in combination with oxaliplatin reduces the progression of CT26 colorectal tumors by down-regulating aerobic glycolysis and glutaminolysis, and increasing oxidative phosphorylation in the mitochondrial electron transport chain which results in reduced ATP production, increased oxidative stress, and apoptosis (Bianchi et al., 2015). In murine 4T1 breast cancer cells, PF increases the phosphorylation of the pro-proliferative but stress-sensitizing Akt and S6 kinases, and increases oxidative stress, caspase-3 cleavage, DNA damage, and apoptosis (Lee et al., 2012). The PF-induced sensitization of mesothelioma cells to cisplatin is mediated by the AMPK dependent activation of the ATM/Chk2/p53 signaling cascade (Shi et al., 2012). In 4T1 breast cancer and B16 melanoma cells fasting causes the SUMO2/3-dependent sumoylation of the DNA polymerase REV1, resulting in the release of p53 and pro-apoptotic gene expression, and the induction of apoptosis in these cells (Shim et al., 2015).

Many oncogenes are tyrosine kinases and thereby provide a target for cancer treatment. In *in vitro* and xenograft models PF potentiates the growth inhibiting efficacy of tyrosine kinase inhibitors by inhibiting MAPK signaling and the E2F-dependent transcription (Caffa et al., 2015). In a subcutaneous non-small cell lung cancer xenograft model, crizotinib or fasting effectively reduced tumor progression but the combination of PF with crizotinib was more efficient than both singular treatment options.

Similar results have been demonstrated in a colorectal cancer xenograft model for the tyrosine kinase inhibitor regorafenib (Caffa et al., 2015).

In summary, these results demonstrate that reducing glucose, amino acids and growth factors protects the organism and simultaneously reduces tumor progression by generating a challenging environment for the survival of malignant cells, particularly in combination with commonly used chemotherapeutic drugs.

4. Dietary preconditioning against surgical stress

In addition to its beneficial effects in the context of cancer prevention and treatment, DR is also associated with resistance to a number of clinically relevant acute stress events, including heart attack, stroke and organ transplantation. Unfortunately, these events are in most cases unpredictable and thus not amenable to DR-based preconditioning interventions. However, in a number of clinically relevant instances, namely in the context of elective surgery, such acute stress events do occur in a known time frame conducive to dietary preconditioning.

Surgery is an inherently stressful process. In addition to an incision, disruption of local blood flow, damage to underlying tissues and activation of local inflammatory mediators, local damage also engenders systemic neuroendocrine and metabolic changes that can affect blood flow, coagulation and immune function throughout the body. Many surgical procedures also involve purposeful, temporary cessation of blood flow to targeted organs, for example to the heart during open heart surgery, or the kidneys during abdominal aortic aneurysm repair. Transplanted organs, vein grafts and skin flaps also experience varying times without blood flow depending on the surgical procedure.

Lack of blood flow to a tissue, known as ischemia, deprives cells of oxygen and nutrients normally supplied by the blood, preventing efficient ATP generation via mitochondrial oxidative phosphorylation while allowing a build-up of toxic byproducts. Restoration of blood flow, or reperfusion, is required for cell viability, but paradoxically also introduces further damage via oxidative stress in part due to the infiltration of pro-inflammatory mediators and leukocytes. This process, commonly referred to as ischemia reperfusion injury (IRI), underlies damage during planned surgical procedures as outlined above, as well as unplanned complications such as heart attacks and strokes resulting from inadvertent thrombotic events or disruption of plaque material from a blood vessel, which can become lodged elsewhere and prevent adequate blood flow to the heart or the brain.

Given its importance as a major mechanism of damage during multiple forms of acute surgical stress, as well as in chronic diseases such as peripheral artery disease commonly associated with type II diabetes, ischemic injury has been studied extensively in pre-clinical models including *in vitro* cell based models in which cells are deprived of oxygen and/or nutrients, and *in vivo* in multiple tissues in rodents including liver, kidney, brain and heart. While much of this research has been geared toward elucidating underlying molecular mechanisms in order to treat associated injury after it occurs for practical translation to the treatment of heart attack and stroke, comparatively little has been designed to understand ways to ameliorate IRI in cases where it can be prevented, for example in the context of major surgery described above.

4.1. Fasting

Studies of preoperative fasting in rats were the first to provide the proof-of-concept evidence that fasting has protective effects against IRI damage to multiple tissues. For instance, in a rat *ex vivo* isolated perfused heart IRI model, 16 h of fasting protected from cel-

lular damage (Schneider and Taegtmeier, 1991), while 2 day fasting in a model of rat brain ischemia reduced neuronal death (Marie et al., 1990). Similarly, in a rat model of liver transplantation, fasting the donor animal prior to the operation resulted in reduced organ damage and a higher chance of survival for the recipient animal (Sumimoto et al., 1993).

More recent studies in multiple preclinical *in vivo* IRI models in rodents have confirmed the effects of preoperative fasting in protection from organ injury to liver, kidney and brain (Mitchell et al., 2010; Varendi et al., 2014; Verweij et al., 2011) and begun to shed light on the mechanistic basis of protection. For example, protection from kidney and liver IRI by 2–3 days of fasting correlates with differential expression of antioxidant enzymes (Verweij et al., 2011) as well as reduced levels of anabolic hormones including insulin and IGF-1, while at the same time increasing sensitivity to these pro-survival factors (Mitchell et al., 2010). Activation of autophagy, possibly due to de-repression upon reduced insulin/IGF-1/mTORC1 signaling, is another common theme in protection. For example, in a mouse model of myocardial IRI, alternate day fasting for 6 weeks protected the myocardium through the transcriptional activation of autophagy, resulting in a reduced infarct size (Godar et al., 2015). Autophagy has also been shown to provide organ protection in the context of renal IRI (Jiang et al., 2010), while the mTORC1 repressor Tsc1 confers neuroprotection in a model of acute ischemic stroke by inducing autophagy (Papadakis et al., 2013). Despite preclinical data supporting fasting as a way to mitigate IRI injury to multiple organs *in vivo*, fasting in the context of surgery remains strictly as NPO after midnight, while general strategies to mitigate IRI are lacking (Mitchell et al., 2013).

4.2. Other forms of DR

While fasting can rapidly precondition against acute surgical stress in rodents, other forms of dietary restriction also lend protection in preclinical models of IRI. Two of the earliest demonstrations that long-term CR (lasting 3 months or more) confer resistance to clinically relevant acute stressors were performed in models of stroke and myocardial infarction (Chandrasekar et al., 2001; Yu and Mattson, 1999). Shorter periods of more severe CR, such as one or two weeks of 50% CR, also protect from liver and kidney IRI (Mitchell et al., 2010; Robertson et al., 2015), as do regimens involving total protein or essential amino acid deprivation (Harputlugil et al., 2014; Hine et al., 2015; Peng et al., 2012; Robertson et al., 2015).

Mechanistically, the protection afforded by protein and essential amino acid restriction appears to overlap that of fasting, for example in its association with reduced circulating growth factor signaling through insulin, IGF-1 and leptin (Harputlugil et al., 2014; Robertson et al., 2015). In the liver, protein restriction leads to improved hepatic insulin sensitivity prior to ischemia and increased pro-survival signaling through the Akt pathway after reperfusion, resulting in increased hepatocellular stress resistance. Decreased mTORC1 signaling, likely a result of reduced growth factors, is required for protection in this model (Harputlugil et al., 2014). In the context of protection afforded by removal of the essential amino acid tryptophan, the amino acid deprivation sensor GCN2 is required for protection (Peng et al., 2012). Mechanistically, this correlates with an increase in expression of ATF4 target genes downstream of GCN2 activation, including those involved in oxidative stress resistance, as well as a GCN2-dependent decrease in circulating IGF1. Although it remains incompletely understood how GCN2 activation mediates downstream protective effects, it is clear that the GCN2 and mTORC1 amino acid sensing pathways are closely connected with cellular stress resistance mechanisms that play a role in preconditioning against IRI.

Restriction of the non-essential amino acid cysteine, on the other hand, is associated with protection from surgical stress via a different mechanism: stimulation of endogenous hydrogen sulfide (H₂S) production (Hine et al., 2015). Hydrogen sulfide is an environmental toxin at high doses, but is an endogenous metabolite with desirable pro-longevity and pro-stress resistance effects at lower doses (Wang, 2012). H₂S is produced by enzymes in the transsulfuration pathway, including cystathionine gamma lyase which is upregulated upon cysteine restriction and more generally upon CR, PR and MR. H₂S likely mediates its protective benefits through a number of molecular mechanisms, including direct antioxidant effects as well as post-translational modification of protein targets by sulfhydration, resulting in a reduction in inflammation and increased antioxidant protection (Hine et al., 2015; Hine and Mitchell, 2015). In the context of simulated IRI in cultured cells, protection by H₂S requires the mitochondrial complex II-like variant SQR, which can use H₂S as an electron donor potentially to maintain mitochondrial electron potential. While constitutive mTORC1 activation represses DR-mediated CGL expression and H₂S production, further research is required to explore the upstream mechanisms of nutrient sensing required for increasing endogenous production, as well as downstream molecular mechanisms of its pleiotropic beneficial effects on stress resistance and longevity.

5. Fasting and its clinical efficacy

5.1. Chemotherapy

Several studies indicate that fasting could potentially be utilized in the clinic to treat diseases and promote health but additional studies are required before fasting-mimicking diets can be included in standard cancer therapies. A randomized clinical trial focused on weight loss in young overweight women demonstrated that 2 days of IF (500 kcal/day) per week and chronic CR equally reduce metabolic disease biomarkers (Harvie et al., 2011). Water-only fasting for 10–14 days followed by an approximately 6–7 days lasting low-fat, low-sodium vegan-based refeeding period reduces systolic blood pressure more than 2-fold compared to a vegan low-fat, low salt diet combined with exercise (Goldhamer et al., 2001; Goldhamer, 2002). Consuming 350 kcal/day, an almost fasting-like approach due to the drastic calorie reduction, has been considered safe for over 2000 participants with chronic diseases and at discharge the main disease-related complaints were significantly improved in fasting but not non-fasting patients (Michalsen et al., 2005).

No randomized clinical trial has (yet) evaluated the effect of CR, IF or PF in cancer prevention, although both preclinical and clinical research indicate the application in prevention and/or treatment of human cancers. PF, but also fasting-like dietary regimens, can have pronounced effects on glucose, IGF-1, insulin, IGF1BP1, and ketone body levels (Fontana et al., 2008; Mercken et al., 2013), changes which have been associated with a protective environment for normal cells while creating an unfavorable metabolic environment for precancerous and/or cancer cells. In a pilot clinical trial focused on a fasting-like dietary intervention in humans, three monthly cycles of a fasting-mimicking diet (FMD) followed by normal caloric intake decreased risk factors/biomarkers for diabetes, cardiovascular disease and cancer, supporting the use of FMDs to promote healthspan (Brandhorst et al., 2015). Although not significant, mesenchymal stem and progenitor cells in the peripheral blood mono-nucleated cell population showed a trend for an increase at the end of FMD cycle, in line with the induction of stem cells in mice (Brandhorst et al., 2015; Cheng et al., 2014; Tinkum et al., 2015). In the FMD study, fasting glucose and IGF-1 levels remained significantly reduced even after resuming their normal

diet following the final FMD cycle which is noteworthy given that elevated circulating IGF-1 levels are associated with an increased risk of developing certain malignancies, including prostate, colorectal and breast cancer (Chan et al., 1998; Hankinson et al., 1998; Ma et al., 1999). Although severe IGF-1 deficiency caused by growth hormone receptor deficiency (GHRD) known as Laron Syndrome leads to growth defects in humans, individuals with GHRD rarely develop cancer (Guevara-Aguirre et al., 2011; Steurman et al., 2011). On the other hand, acromegaly associated with high concentrations of insulin-like growth factor-I due to growth hormone stimulation, has been associated with an increased risk of colorectal cancer and breast cancer in some studies and less consistently with prostate, thyroid, and hematological malignancies (Jenkins, 2004; Kauppinen-Makelin et al., 2010). In a population-based study of over 6000 American adults, 50–65 year-old respondents with the highest circulating IGF-1 levels experienced a 75% increase in overall mortality and a 4-fold increase in cancer death risk compared to the low IGF-1 cohort (Levine et al., 2014).

In cancer treatment, a few studies now begin to explore the fasting-induced protection against chemotoxicity-related side effects. In a small study of 10 patients with a variety of malignancies that voluntarily fasted for up to 180 h, a reduction in chemotherapy-associated side-effects including vomiting, diarrhea, fatigue and weakness was observed. In cases where cancer progression could be monitored, no evidence was found that fasting interferes with chemotherapy efficacy or protects the tumors (Safdie et al., 2009). In a dose-escalation study of 24–72 h of fasting prior to platinum-based chemotherapy in 20 cancer patients, IGF-1 levels decreased and 72 h of fasting was considered safe and feasible (Dorff et al., 2016). The results from a phase I clinical trial indicate that 72 h of PF in combination with chemotherapy were associated with normal lymphocyte counts and maintenance of a normal lineage balance in white blood cells, analogous to the PF effects on the murine immune system (Cheng et al., 2014; Safdie et al., 2009). In a pilot study, 7 out of 13 women diagnosed with HER2-negative stage II/III breast cancer randomized to fast 24 h before/after receiving neo-adjuvant (docetaxel/doxorubicin/cyclophosphamide) chemotherapy reported that PF was well tolerated (de Groot et al., 2015). Notably, PF protects from the chemotherapy-dependent reduction in erythrocyte and thrombocyte counts and possibly DNA-damage in healthy cells when compared to the non-fasted subjects, and no changes in leukocyte or neutrophil counts which may be associated with a pegfilgrastim-induced production of white blood cells (de Groot et al., 2015). However, the use of the antiemetic drug dexamethasone in this trial may explain why glucose increased despite 24 h of fasting which likely attenuated some of the benefits of starvation, including a more prominent IGF-1 reduction (de Groot et al., 2015). Alternatively, 48 h of fasting may not be sufficient for humans to optimize the differential stress resistance or sensitization of normal and malignant cells. Despite the findings outlined above, it is noteworthy that data on humans remain limited and not confirmed in well-conducted and sufficiently large randomized clinical trials. However, this is now being addressed by a number of clinical trials that test the effects of fasting or fasting mimicking diets on humans and the diet-induced protection of patients from the side effects of chemotherapy while sensitizing cancer cells to the treatment.

5.2. Surgery

Similar to chemotherapy, no randomized clinical trial has yet evaluated the potential of specialized preoperative diets such as DR to improve surgical outcome. Currently preoperative guidelines recommend an overnight fast prior to the day of surgery to prevent aspiration pneumonia while the patient is under anesthesia (American Society of Anesthesiologists, 2011). Unintended delays

in the start of the surgery itself can extend the time spent in a fasted state to a day or slightly longer. However, while the time frame necessary to achieve DR-related benefits in humans remains unknown, the sufficiency of such short time frames to achieve maximal benefits as observed upon DR in preclinical models is considered highly unlikely. Furthermore, because the danger of aspiration is associated mainly with intake of solid foods, drinking of clear liquids including carbohydrate-rich beverages is increasingly allowed and in some cases recommended up to several hours before anesthesia in order to prevent thirst, hunger and insulin resistance after the operation. Although this current trend of preoperative carbohydrate loading appears to go in the opposite direction of preclinical evidence presented in this review, it is not necessarily mutually exclusive with the concept of dietary preconditioning, which can be activated by protein/amino acid restriction independent of carbohydrate intake, and which is associated with at least some limited “memory” beyond the refeeding period (Mitchell et al., 2010). Future clinical studies are thus required to address the question of optimum feeding strategy, including both composition, timing, and the potential role of preoperative carbohydrate loading, as a potential prophylactic strategy to protect tissues and organs from surgical stress.

Despite the encouraging results from preclinical studies on the protective effects against surgical stress, lack of evidence of efficacy in humans combined with concerns about potential side effects of preoperative DR currently hinders clinical testing. Based on the experimental literature, major concerns about DR in the operative setting include compromised immune responses and impaired wound healing. While the ability of DR to dampen pro-inflammatory responses likely contributes to its beneficial effects in the context of sterile inflammatory models such as IRI (Chandrasekar et al., 2001), the same effects could in principle hinder the ability of the body to fight off hospital-acquired infections, one of the most important risk factors for people undergoing surgery. However, although DR clearly modulates the immune response, it does not necessarily hinder adaptive responses to infectious agents. For example, in a model of experimental cerebral malaria, DR during the course of blood-stage infection promotes adaptive immunity and parasite clearance by the spleen while at the same time limiting maladaptive proinflammatory T cell-mediated reactions elsewhere in the body (Mejia et al., 2015). Furthermore, although long-term CR is associated with poor wound healing, dietary preconditioning against surgical stress is followed by unlimited access to a complete diet immediately after surgery, and is not associated with any problems in wound healing.

Most importantly, although the concept of preoperative DR as a prophylactic intervention against surgical stress including potential complications has not specifically been tested, intake of low calorie diets prior to bariatric surgery for the purpose of reducing liver weight and facilitating the surgical procedure is already standard practice in the context of bariatric surgery. While improving perioperative outcome is difficult in this low-risk surgery, the lack of problems with wound healing or infection is notable (Van Nieuwenhove et al., 2011). Although hopeful, future studies on efficacy as well as safety in high-risk surgery groups is nonetheless required.

6. Conclusions

Dietary interventions including CR, PR, MR, IF/ADF and PF have been shown to induce substantial health benefits in the majority of the investigated laboratory animal models. Yet, due to its chronic nature, long-term CR is not feasible for the great majority of subjects and may induce some detrimental effects by negatively affecting wound healing. Brief periods of fasting followed by nor-

mal refeeding can promote long-lasting health benefits without the need of chronic daily or every-other day restriction, while reducing or even eliminating some of adverse effects of CR. Despite numerous advantages, extreme water-only fasts could cause adverse effects, including the exacerbation of previous malnourishments and dysfunctions. These concerns are now being addressed by implementing newly designed fasting-mimicking dietary interventions aimed to induce PF-like effects while minimizing the risk of adverse effects and the burden of complete food restriction. In C57Bl/6 mice, bi-monthly cycles of a 4 day long diet that mimics the effects of fasting (Fasting Mimicking Diet, FMD) extends healthspan and longevity, promotes hippocampal neurogenesis, lowers visceral fat, reduces skin lesions, rejuvenates the immune system, and retards bone mineral density loss in old mice (Brandhorst et al., 2015). The FMD cycles started at middle age reduces tumor incidence, delays their onset, and causes a major reduction in the number of lesions, which may reflect a general switch from malignant to benign tumors. Of note, the FMD also has potential implications in cancer treatment: in a recently published study, the combination of chemotherapy and FMD in mice delayed breast cancer and melanoma progression, and increased the levels of bone marrow common lymphoid progenitor cells and cytotoxic CD8⁺ tumor-infiltrating lymphocytes. In the breast cancer model, this effect was partially mediated by the downregulation of the stress-responsive enzyme heme oxygenase-1 in cancerous cells (Di Biase et al., 2016). Furthermore, diets reduced in or lacking protein or essential amino acids have similar beneficial effects on metabolism and stress resistance (Robertson et al., 2015), and because they can be fed on an *ad libitum* basis, may also function in the context of preconditioning prior to elective surgery. Taken together, these results indicate that PF and FMD have the potential to play an important complementary role in medicine by increasing stress resistance, promoting disease prevention, enhancing disease treatment, stimulating stem cell-based regeneration and delaying the aging process.

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