MINIREVIEW

Calories, Cell Proliferation, and Proviral Expression in Autoimmunity and Cancer

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Healthful Consequences of Reducing Dietary Calories. Reduced calorie intake (RCI) to levels 20–40% less than *ad libitum* intake without essential nutrient deficiency extends the latency to onset and reduces the frequency of neoplastic and autoimmune disease in rodents, and extends the healthful longevity of many species across wide phylogenetic differences (1–4). The beneficial consequences of RCI have been demonstrated in disease pattern surveys of large populations of outbred and inbred rats, and long-lived inbred and hybrid mice fed semipurified diets which vary only in caloric level. In these surveys, cumulative frequencies of mortality due to neoplasia and other diseases among calorie-restricted cohorts were lower and maximum longevities were extended.

Healthful longevity has also been extended and onset of disease has been delayed by RCI in short-lived inbred, hybrid, and mutant mice. Mice of short-lived strains are genetically prone to develop and die at a young age of a progressive disease syndrome that ordinarily develops with advanced age. Diseases of short-lived mice delayed or prevented by reducing dietary calories include the systemic amyloidosis of senescence-accelerated mice (5), the systemic lupus erythematosus-like syndrome of B/W F_1 mice (6, 7), the breast cancer of C3H mice (8–13), the nephrophthisis of *kd/kd* mice (14), the lymphoproliferative syndrome of autoimmune-prone MRL mpj lpr/lpr mice (15, 16), and the thymic lymphosarcoma of AKR mice (17). The discussion presented here concerns observations of extended healthful longevity in three of these short-lived cancer-prone or autoimmunity-prone strains of mice.

Extension of healthful longevity depends quite specifically on energy restriction and is not the consequence of altered dietary composition. Although incidences of diseases can be altered by variation in both type and quantity of certain dietary variables independent of calorie level, restriction of or variation in the type of dietary fat (10, 18), protein (7, 19–21), or carbohydrate (22, 23), or supplementation with vitamin E (24) or other antioxidants (25) or overall vitamin supplementation (26) without restriction of calories does not increase the maximum life span of rodents.

Successful promotion of healthful longevity by RCI in diverse experimental settings implies a fundamental impact on aging and disease resistance, with repercussions involving neuroendocrine, immunologic, and metabolic systems. Involution of thymus-related immunologic efficiency and onset of reproductive senescence are delayed by RCI (2, 27–29). Energy metabolism may be altered by RCI with reduced free radical production and increased free radical detoxification (30, 31). Protective processes, such as the enzyme-mediated repair of DNA, may be significantly promoted by RCI (32). The extent to which multiple systems are influenced by RCI, and the phylogenetic independence of its efficacy, suggests that restriction of dietary energy evokes an evolutionarily selected adaptive response to variances in food availability and periodic food deprivation. As discussed in this Minireview, the principle site of impact of this RCI-evoked adaptive response may be at the level of proliferative systems.

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Cell Proliferation Promotes Mutagenesis

Cell division allows for mitotic recombination, the fixation of mutations, the activation of oncogenes, the expression of proviruses, and the inactivation of tumor suppressor genes (33–38). Cancer cells contain multiple genetic lesions, including mutations, translocations, oncogene amplifications, and the inactivation of tumor suppressor genes. All such procarcinogenic events require cell division, and increased cell division increases cancer risk (33–35). Increased cell proliferation may increase deteriorative aging, reduce adaptability to environmental stimuli, and accelerate the acquisition of genetic lesions and altered expressions, which contribute to the development of disease.

Influence of Calories on Cellular Kinetics and Responsiveness

Reduced calorie intake may exert its influence preferentially at the stage of initiation of cell replication by reducing the basal proliferative rates of potentially proliferative cell populations while preserving or enhancing cellular responses to an inductive stimulus. Such an adaptation would accord with RCI's beneficial effects of delayed programmatic aging and increased resistance to disease.

Cell proliferation during the peripubertal growth of adolescent rodents is reduced when feeding is restricted (39). Organ and body weights are reduced by restricted feeding, but organ to body weight ratios of restricted animals are similar to those of *ad libitum*-fed controls. Maintenance rates of cell proliferation in adult rodents may also be lowered by RCI (40, 41), but others find no such influence (39).

Adaptability to environmental stimuli is maintained and may be enhanced with RCI by preserving adequate or even greater inducible cellular responses, such as during regeneration of removed hepatic parenchyma or as required for immunologic defense. Mice fed an RCI level have reduced cell numbers in spleen and lymph nodes, are leukopenic and lymphopenic, and have lower unstimulated natural killer cell activity than *ad libitum*-fed controls (1, 13, 42–44). In spite of this, lectin-induced lymphocyte proliferation, poly(I-C)-induced natural killer cell activity, production of and responsiveness to interleukin 2, and induced T lymphocyte killing of tumor cells are all augmented by RCI (1, 31, 42–44).

A rodent model representing events associated with induced, regulated cell proliferation involves hepatic regeneration in response to partial hepatectomy. This compensatory increase in hepatocellular replication is regulated by circulating mitogenic factors such as epidermal growth factor, transforming growth factor-α, and hepatopoietin A, and is accompanied by elevated expression of cell cycle-associated genes such as c-*fos*, c-*myc*, and c-Ha-*ras* (45, 46). The hepatocellular proliferative burst eventually restores the removed parenchyma.

Rodents fed an RCI level respond to partial hepatectomy with an equivalent or greater hepatocellular proliferative burst than *ad libitum*-fed controls (47). Although a comparable profile of oncogenes is activated during hepatic regeneration regardless of dietary energy level, mRNA expression levels of c-*fos* and c-Ki-*ras* are substantially reduced by lowering calorie intake (47).

Influence of Calories on Proviral Expression

Pathogenesis of strain-specific disease of some short-lived mice is coupled to retroviral expression. Efficient retroviral expression *in vitro* proceeds only when cultured host cells are synthesizing DNA and actively dividing (36–38). Since retroviral expression *in vitro* is more efficient when host cells are cycling and not stationary, exposures such as RCI that impair retroviral-associated disease may do so by lowering host cellular kinetics *in vivo*, reducing the efficiency of retroviral replication, and preventing the activation of subsequent genetic events required for the acquisition of a pathologic phenotype. Lowering dietary calories suppresses proviral transcription and abrogates retroviral-associated tumorigenesis in both mammary adenocarcinoma-prone C3H/Ou mice and thymic lymphosarcoma-prone AKR mice (8–13, 17).

Influence of Calories on Lymphomagenesis

Thymic lymphomagenesis in AKR mice requires the early expression of ecotropic murine leukemia virus (MuLV) which peaks in intensity around 2 months of age, and the subsequent emergence of a genomic-length, recombinant MuLV which is distinguished by an ability to form cytopathic foci in cultured mink lung cells (48–50). Subgenomic-length mink cytopathic focus-forming (MCF) MuLV mRNA is expressed perinatally in many tissues, but genomic-length MCF MuLV mRNA first appears around 3–4 months of age. MCF MuLV virus isolation is possible only when AKR mice are at least 5 months old, and then only from thymic or lymphoma tissue.

By reducing dietary calories, thymic expression of subgenomic MCF MuLV mRNA is uniformly suppressed among 6- and 8-week-old AKR mice, the frequency of appearance of genomic-length MCF MuLV transcripts is reduced, the latency to median lymphoma incidence is extended by greater than 3 months, the cumulative tumor incidence is reduced by 28%, and the median life-span of RCI mice is increased by approximately 50% (17). Survival curves for *ad libitum* and RCI dietary cohorts are significantly different ($P < 0.0001$), with *ad libitum*-fed mice experiencing a three times greater risk of lymphoma mortality (17).

Influence of Calories on Breast Tumorigenesis

Mammary proviral transcription of the mouse mammary tumor virus (MMTV) is essential for the regular development of mammary adenocarcinoma in C3H/Ou mice (51). Mammary tumors in C3H/Ou mice develop through morphologically definable stages, including the development of preneoplastic, hyperplastic alveolar nodules. Protooncogene *Wnt* and *ras* activation has been demonstrated in mouse mammary hyperplasia and tumors, and hyperplasia develops with transfection of *ras in vitro* and in mice transgenic for *Wnt* or transforming growth factor-α (52–56). Reduced epithelial proliferation and suppressed MMTV transcription with RCI may reduce the possibility of insertional activation of protooncogenes, prevent the development of hyperplastic lesions, and thereby abrogate the genesis of mammary adenocarcinoma.

By reducing dietary calories, the mean mammary DNA-labeling index of RCI mice is lowered, indicating reduced epithelial division, onset of measurable mammary MMTV mRNA expression in C3H/Ou mice is delayed, maximal proviral transcription is rarely achieved, and mammary tumorigenesis is strictly impaired (11–13; R. W. Engleman, N. K. Day, R. A. Good, personal communication, 1992). For example, the mean mammary DNA-LI is 8-fold greater and the mean mammary MMTV mRNA level is 5-fold greater in *ad libitum*-fed mice compared with similar determinations in age-matched RCI mice (11–13; Engleman *et al.*, personal communication, 1992). Median mammary tumor incidence among *ad libitum*-fed mice is reached when mice are 46 weeks old, and greater than 95% develop mammary tumors within 66 weeks of age. Most C3H/Ou mice remain refractory to mammary tumor development when dietary calories are controlled. If mammary tumors develop among RCI mice, they do so only after a prolonged latency, typically when mice are older than 75 weeks, and cumulative mammary tumor incidence remains less than 15%.

Transcription of MMTV and C3H/Ou mammary tumorigenesis are hormone responsive. Glucocorticoid and progesterone augment MMTV transcription *in vitro* (57). Prolactin regulated MMTV transcription *in vitro*, increases mammary epithelial proliferation and MMTV transcription *in vitro*, is positively associated with risk for mammary tumor formation, may be reduced by lowered dietary energy levels, and, hence, may be a potential mediator between dietary calories and mammary tumor risk (9, 12, 58).

MMTV transcription and C3H/Ou mammary tumorigenesis are also influenced by parity. Proviral MMTV transcription rises abruptly during late gestation and early lactation and drops precipitously during mammary involution, but remains somewhat elevated among *ad libitum*-fed compared with RCI uniparous mice (13, 58, 59). Even after the transient induction of very high levels of MMTV mRNA during early lactation in both *ad libitum* and RCI mice, mammary MMTV transcription among RCI mice postpartum is again suppressed to levels 4- to 5-fold less than those of *ad libitum*-fed mice, and protective reduction of mammary tumor risk by RCI is preserved (13).

Mammary glands of *ad libitum*-fed C3H/Ou mice are highly proliferative and frequently exhibit overt hyperplastic alveolar nodules. Lowering calorie intake reduces the rate of mammary epithelial cell division (Engelman *et al.*, personal communication, 1992). That this suspension of cell proliferation occurs without detriment to the induction of functional lobuloalveoli at lactation is inferred by the comparable levels of mammary α-casein mRNA expressed, and the comparable number and size of litters delivered and nursed effectively by both *ad libitum*-fed and RCI mice when the nutritional demands of gestations and lactation are met (13; Engelman *et al.*, personal communication, 1992).

The abrogation of C3H/Ou mammary tumorigenesis by RCI may be attributable to modulated serum prolactin activity, reduced rates of mammary epithelial proliferation, a consequent reduction in MMTV transcription, and the prevention of MMTV insertional activation of protooncogenes.

Influence of Calories on Development of Autoimmunity

Controlling dietary calories curtails the onset of autoimmunity and extends healthful life span in autoimmune-prone strains of mice, which develop a disease similar to systemic lupus erythematosus (6, 7). Reduced calorie intake lowers cellular proliferation rates within the thymus, spleen, and mesenteric lymph nodes of these mice, delays the appearance and growth of Lyt-1+ B lymphocytes, a subpopulation linked to autoantibody production, and suppresses the production of anti-DNA antibodies and immune complexes (6, 60, 61). Expression of genomic-length MCF MuLV transcripts is indicated in the etiology of murine lupus (62, 63). Since lowered dietary calories reduce expression of the major retroviral envelop glycoprotein gp70 in the sera of autoimmune-prone B/W F_1 mice (63), and lowers cellular replication in lymphoid organs in autoimmune-prone strains (40), the extension of healthful longevity in autoimmune-prone mice may in part reflect reduced cellular proliferation, inefficient proviral transcription, lowered expression of retroviral protein and formation of immune complexes, delayed glomerular injury, and delayed activation of subsequent genetic events required for the upswing in autoimmune phenomena.

Implications of Reducing Dietary Calories

Reducing dietary calories may be one of the most promising neglected preventive medical strategies. Excess calorie intake leads to obesity and increased mortalities from cancers of the uterus, gallbladder, kidney, stomach, colon, and breast (64). Women 40% above desirable weight have a 55% greater mortality from cancer than individuals of recommended body weight, and similarly obese men have a 33% increased risk of cancer mortality (64). Elevated caloric intake may be the most striking rodent carcinogen ever discovered. Increasing the caloric intake of rodents by about 20% above optimal causes a remarkable decrease in longevity and an increase in cancer, autoimmunity, and other diseases. In some short-lived cancer-prone or autoimmunity-prone strains of mice, RCI prevents development of disease, perhaps in part because basal proliferative rates of potentially proliferative cell populations are reduced, limiting the acquisition of genetic lesions. Understanding the adaptive response evoked by reduced calorie intake will aid in defining cellular and genetic mechanisms which contribute to healthful longevity and aid in determining their accessibility to surrogate inductants (65).

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