

Editor's Corner

Cancer and aging

More puzzles, more promises?

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In this issue of *Cell Cycle*, a new paper shows that metformin, an oral antidiabetic drug that activates AMP-activated protein kinase, prolongs both mean and maximal life span and prevents reproductive aging of female mice. Unexpectedly, metformin did not decrease the incidence of cancer in this mice strain. Here, we discuss the relationship between aging and cancer, the mechanism of metformin action, and the prospects of using this compound for life span extension in humans.

Introduction: Metformin, a Potential Anti-Aging Drug?

There are no known interventions—certainly no commercial drugs—that are proven to substantially slow the aging process in humans.¹ Indeed, some gerontologists believe such drugs can never be developed because aging is caused by a random accumulation of damage, some of which is inevitable and irreversible.

The paper in this issue of *Cell Cycle* by Anisimov and colleagues describes the effects of metformin, an anti-diabetic drug that abrogates insulin-resistance, on life span in mice. Female mice were fed metformin in drinking water beginning at 3 months of age, using a dose that is less than that commonly used in the clinical treatment of diabetes (adjusted for the body size of mice). Although this study was restricted to female mice from a single strain (SHR, an apparently outbred strain), the effects were impressive. Metformin treatment increased mean life span by >37% and increased maximum life span by >10 months. Further, metformin extended the mean life span of the longest-living animals in the study population (the last 10% of survivors) by >20%. Consistent with its life span-extending effects, metformin also prevented reproductive aging (degeneration of the estrous cycle). Surprisingly, however, metformin failed to decrease the incidence of malignant tumors. In both the control and metformin-treated groups, the primary types of cancer were mammary carcinomas and leukemias, neither of which was affected by metformin feeding. However, metformin was especially effective

at prolonging the life span of those animals in the population that did not succumb to cancer. Thus, metformin extended the mean life span of tumor-free mice by an impressive 70.3% (from 290 to 494 days).

Earlier studies from the same group showed that metformin modestly extended the life span (by 8%) of transgenic female mice (strain FVB/N) carrying a HER-2/neu oncogene, which predisposes the animals to mammary cancer.² In these mice, metformin decreased cancer incidence and delayed cancer onset, suggesting it might extend life span by suppressing the development of cancer. These results are consistent with results reported approximately 30 years ago showing that phenformin (an analog of metformin) suppressed chemically (DMBA)-induced mammary tumor development in rats,³ and reduced spontaneous tumor incidence in mice, resulting in a 23% increase in mean life span.⁴ Recently, metformin was shown to specifically impair the growth of tumor cells that lack p53 function, suggesting that this drug is selectively toxic to p53-deficient cells.⁵

In the study by Anisimov and colleagues, metformin did not affect cancer incidence or latency. This apparently negative result is remarkable for two reasons. First, it demonstrates that metformin can prolong life and presumably delay aging by a mechanism(s) unrelated to its ability to suppress cancer. Second, this finding indicates that cancer and aging can be dissociated.

Cancer is an Age-Related Disease

Cancer incidence rises exponentially with age in humans and most other mammals. This trend should not be confused with the notion that cellular senescence is a barrier to the development of cancer. Cellular senescence is the irreversible cell cycle arrest that prevents damaged or pre-malignant cells from proliferating, thereby preventing them from forming malignant tumors. In other words, cellular senescence prevents cancer, whereas aging tissues, which accumulate senescent cells, promote cancer.

Paradoxically, senescent cells might contribute to the rise in cancer that occurs with age, and might do so by altering the tissue microenvironment. Senescent stromal cells produce enzymes, growth factors and inflammatory cytokines that can stimulate neighboring pre-malignant or dormant tumor cells to acquire malignant phenotypes and eventually form lethal cancers.⁶⁻¹⁴ Thus, age-related cancers might arise in part from a combination of the age-dependent

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increase in mutations and the degradation of the normal tissue milieu. Consistent with a systemic link between aging and cancer, calorie restriction is known to both slow aging and delay cancer in rodents.¹⁵⁻¹⁸ Likewise, long-lived mice have a lower incidence of cancer compared to shorter-lived mice,^{19,20} and centenarians, people who age slowly, are generally remarkably cancer-free.²¹ Indeed, many interventions that slow aging also delay cancer, and many interventions that accelerate aging (e.g., many progeroid syndromes) also increase the cancer incidence. Nonetheless, there are notable manipulations or circumstances that dissociate aging and cancer.

Relationships Between Aging and Cancer

One such manipulation entails altering the activity of the p53 tumor suppressor protein.²² Short forms of p53, namely the naturally occurring p44 isoform and an artificial C-terminal p53 fragment, both of which constitutively elevate p53 activity, shorten life span in mice.^{23,24} Notably, these mice have less cancer, despite their shorter life span, and display phenotypes consistent with accelerated aging. On the other hand, transgenic mouse models in which p53 activity is elevated, but in a regulated manner, show reduced tumor formation without accelerated aging.²⁵⁻²⁷ Finally, some manipulations that increase regulated p53 activity delay cancer and increase lifespan.²⁸ This last situation is that which is most expected: prevention of cancer, a major cause of death in mice, is expected to prolong life span.

Why do some manipulations of p53 activity shorten life span, while decreasing cancer? One possibility is that these manipulations substantially increase the senescence and/or apoptosis of damaged or premalignant cells, which in turn degrades tissue integrity, despite suppressing cancer. In addition, the p44 isoform increases IGF-1 signaling, which is a conserved pro-aging pathway. It is also noteworthy that IGF-1 signaling activates the TOR pathway, which is inhibited by metformin.²⁹

Why did Metformin Extend Life Span without Decreasing Cancer?

The finding by Anisimov and colleagues that metformin did not suppress cancer was unexpected. Consequently, it was even suggested that this result might be simply coincidental, or idiosyncratic to the mouse strain used in this study (this issue). It would be of interest to know whether calorie restriction delays cancer in this particular mice strain. Whatever the case, even if this is an exceptional strain, there must be an explanation for why metformin did not affect the development of cancer.

First, it is notable that in these mice cancer develops relatively late in life. The first tumor-bearing mice died at 457 days of age in the control group, which has a mean life span of 290 days. Metformin increased life span by 37%, but this effect was especially robust in those mice that died first (fast aging mice) and without cancer. Thus, by increasing the life span of fast aging mice, metformin might have allowed them to reach the age at which cancer develops in this strain.

Second, metformin might have pleiotropic effects. For example, metformin might alter the mammary epithelium and bone marrow in young mice, priming them to develop cancer later in life. By activating AMPK, metformin might select for cells that are resistant to AMPK activation and thus TOR inhibition, resulting in a

population of cells that are hypersensitive to IGF-1 signaling, which can drive cancer. Metformin has cytotoxic effects in some cancer cells⁵ but this might be a double-edged sword if more aggressive resistant cells emerge.³⁰ In light of these possibilities, if metformin also delayed cancer by slowing aging, as anticipated a priori, the net result would be zero. If any of these possibilities hold true, metformin might be best administered not at the age of 3 months, as was the case in the Anisimov study, but later in life to minimize early life pleiotropic effects.

Third, it is possible that metformin did not affect a fundamental aging process per se, but rather one or more phenotype closely associated with aging. Consistent with this possibility, metformin did not decrease insulin levels, which rose 10-fold with age in both control and metformin-treated mice. Likewise, metformin failed to alter other parameters that changed with age, such as blood glucose and cholesterol levels and body temperature. Thus, metformin might have only partial anti-aging effects. Metformin might act in a tissue- or cell-specific manner, for example, it might affect the liver but not kidney, or epithelial cells but not stromal cells (or vice versa). Further, the metformin dose might have been insufficient to alter cancer, despite being sufficient to alter other age-related pathology, such as cardiovascular diseases (CVD). By analogy, low doses of aspirin decrease the incidence of CVD, but high doses are needed to reduce colon cancer incidence.

The TOR Pathway and Aging

Metformin is known to activate AMPK,³¹⁻³³ which in turn inhibits TOR (target of rapamycin), thus restoring insulin sensitivity.³³ As recently suggested, activation of the TOR pathway might link cellular senescence, organismal aging and age-related diseases.^{29,34} TOR activation is required for the hypertrophic senescent phenotype that accompanies the irreversible senescent cell cycle arrest.³⁵ Moreover, the TOR pathway has been shown to be an important pro-aging pathway in species as diverse as yeast,³⁶ worms,^{37,38} flies³⁹ and mice,⁴⁰ and to be involved in a plethora of age-related diseases.^{33,41-43}

Further Directions

The finding that metformin can prolong life span without affecting cancer was surprising because, in cancer-prone strains of rodents, metformin both prevented cancer and extended life span. Is it possible that metformin might slow human aging and/or prevent cancer in humans? It has been reported that diabetic patients treated with metformin have a reduced incidence of breast cancer and cardiovascular disease.⁴⁴⁻⁴⁶ What about non-diabetic people? Of note, metformin was shown to restore menstrual function and fertility in patients with polycystic ovary syndrome.⁴⁷ Thus, clinical trials to test the efficacy of metformin in preventing cancer, type II diabetes and menopause may be warranted.

If metformin extends life span by inhibiting the TOR pathway, then direct inhibitors of TOR might likewise be considered for clinical trials. Currently, there are no data regarding whether the TOR inhibitor rapamycin slows aging in mice or humans. But there are a plenty of human and animal data showing that rapamycin can prevent cancer. In cancer prone mice and mice treated with a carcinogen, chronic administration of rapamycin or an analog markedly delayed tumor development.^{48,49} In humans, rapamycin (Sirolimus)

is currently used as an immunosuppressant in renal transplant recipients to prevent organ rejection. In these patients, rapamycin decreased the frequency of new tumors.⁵⁰⁻⁵⁵ In addition, rapamycin was reported to cure some types of pre-existing malignancies.⁵⁶⁻⁶¹ Further, TOR inhibitors increased the progression-free survival of breast cancer patients,⁶² and these inhibitors are approved for the treatment of metastatic renal-cell carcinoma.⁶³ And cancer may be prevented by inhibiting aging.⁶⁴ So rapamycin may be indicated for cancer prevention in humans, and once used for this purpose, might also show anti-aging effects.

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