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Rapalogs in cancer prevention

Anti-aging or anticancer?

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Common cancer is an age-related disease. Slow aging is associated with reduced and delayed carcinogenesis. Calorie restriction (CR), the most studied anti-aging intervention, prevents cancer by slowing down the aging process. Evidence is emerging that CR decelerates aging by deactivating MTOR (target of rapamycin). Rapamycin and other rapalogs suppress cellular senescence, slow down aging and postpone age-related diseases including cancer. At the same time, rapalogs are approved for certain cancer treatments. Can cancer prevention be explained by direct targeting of cancer cells? Or does rapamycin prevent cancer indirectly through slowing down the aging process? Increasing evidence points to the latter scenario.

Cancer is an Age-Related Disease

Common cancers such as lung, breast, prostate, colon, gastric, esophageal, pancreatic, thyroid, brain and certain leukemias, are age-related diseases, meaning that their incidence is dramatically increased with aging and about one third of elderly people die from cancer. In rapidly aging mammals such as mice, cancer develops by the age of 1 to 2 years. In humans, common cancers are delayed and occur toward the end of the life, too. Centenarians, people who live more than 100 years, are especially protected from cancer.[1-3] In long-lived mice, cancer is delayed.[4] In slow-aging naked mole-rats, cancer is uncommon despite high levels of oxidative damage.[5] Also CR slows down aging and delays cancer.[6-14] In contrast, overeating, high caloric food and obesity accelerate cancer.[15]

mTOR in Organismal Aging

So why do overeating, obesity and nutrients accelerate aging? One explanation is that nutrients and insulin activate the nutrient-sensing mTOR pathway. This pathway drives cellular mass growth.[16-19] Growth factors, insulin and nutrients activate nutrient-sensing and growth-promoting pathways, which in turn drive developmental growth. Later in life the same pathway drives aging, which is a continuation of developmental growth.[20-22] In agreement, calorie restriction, which deactivates the TOR pathway, slows growth early in life and delays aging later in life.[10,11] This is simple and straightforward. This predicts that rapamycin would slow down aging and extend life span.[23] In fact, rapamycin extends life span in yeast,[24] Drosophila[25,26] and mice.[27-33] Also, genetic manipulations that decrease the activity of TOR in turn increase life span in diverse species.[34-41]

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mTOR and Cellular Aging (Geroconversion)

In proliferating cells, growth factors (GFs) activate both the growth-promoting mTOR pathway and the cell cycle. Therefore cellular growth is balanced by cell division. When the cell cycle is blocked, yet mTOR is active, cells undergo gerogenic conversion or geroconversion.[42] At first, the arrested cell is not senescent. Overtime, the mTOR pathway converts arrest into senescence.[42-44] Also activation of mTOR converts quiescence into senescence, when the cell cycle is still locked.[45-47] This type of geroconversion may imitate physiological aging of post-mitotic cells in the organism. Aged cells are hypertrophic and hyper-functional.[48,49] In turn, aging cells due to their hyper-functions cause diseases of aging such as obesity, pro-inflammatory syndrome, atherosclerosis, hypertension, neurodegeneration and osteoporosis.[50-55] It is very important to emphasize that geroconversion is not a transition from proliferation to arrest. Geroconversion is a transition from arrest and quiescence to senescence. In the young organism, post-mitotic cells are quiescent, becoming senescent over time. In theory, a proliferating cell may also undergo pro-gerogenic conversion. This condition may be manifested as cancer.

mTOR in Cancer

The PI3K/mTOR is almost universally activated in cancer[56-62] and is a promising therapeutic target.[63-78] The similarity between cancer and aging is not coincidental. Aging can be viewed as "twisted growth," when actual growth is precluded.[43] Cancer is actual growth and proliferation of pro-gerogenic cells (it is sufficient to ensure cell cycle arrest and then gerogenic conversion will occur). Oncogenic proteins such as growth factor-receptors, activated Ras, tyrosine (Src) and serine/threonine kinases, such as Raf, MEK, PI3K, Akt, all activate mTOR. Inactivation of tumor suppressors such as PTEN, NF-1, TSC2 activate the mTOR pathway.[56-62] Inactivation of some tumor suppressors (Rb, p53 and p16) overcomes cell cycle arrest and prevents the senescent phenotype. P53 inhibits mTOR.[79-81] Here it is important to

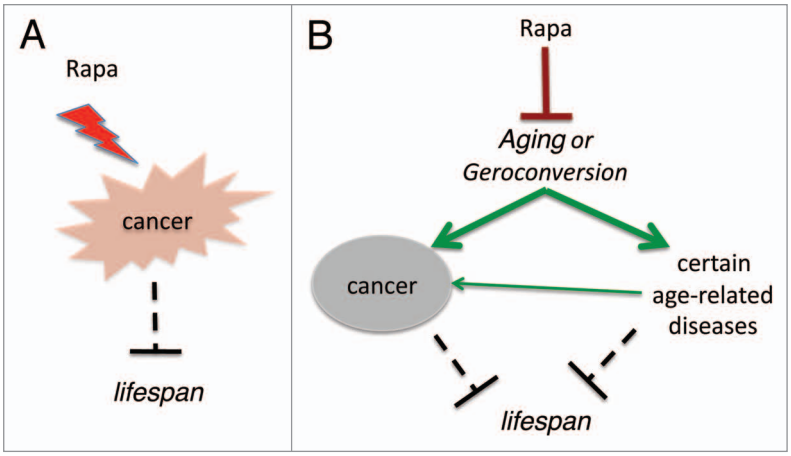

Figure 1. Two models of cancer-prevention by rapalogs. (**A**) Direct anticancer effect. Rapalogs (Rapa) suppress cancer cells, prevent cancer and thus extend lifespan. (**B**) Indirect anticancer effect due to aging-suppression. Rapalogs (Rapa) suppress aging (gerosuppression) and thus prevent cancer and other age-related diseases, extending lifespan.

emphasize that p53 not only causes arrest but also can suppress geroconversion (conversion from arrest to senescence), ensuring instead quiescence.[45,82-93] Therefore, p53 is so often inactivated in cancer cells, which can be viewed as proliferating senescent cells. In aging, the mTOR pathway is activated by signals from other cells and by feedback loops.[94] In cancer, the mTOR pathway is activated by mutations and other stable alterations in upstream oncoproteins/tumor suppressors. Multiple rounds of cellular proliferation and selection transform initially random mutations into non-random activation of the mTOR pathway. Growth-limiting conditions and senescence of normal cells provides such a selective advantage.[94-97] Therapy further drives tumor progression.[98]

Cancer Treatment with Rapamycin

Given the universal activation of the mTOR pathway in cancer, rapalogs are used for cancer treatment.[99-102] Temsirolimus, a prodrug of rapamycin (Sirolimus), became the first rapalog approved for cancer treatment.[103] The uses of rapalogs in the therapies of cancer and other diseases are rapidly increasing.[104,105] Hundreds if not thousands of clinical trials are under the way. Yet, rapalogs (rapamycin and its analogs) are not a panacea. Although effective for approved indications (otherwise the drugs would not be approved), rapalogs still play a modest role in cancer treatment. For one, rapalogs (rapamycin and its analogs) at relevant concentrations are not toxic drugs: they do not kill cells but rather they slow their growth. While this is a disadvantage of rapalogs as anticancer drugs, this is an advantage as cancer-preventive and anti-aging agents. Rapalogs can reverse cell senescence in cancer stroma,[106] potentially contributing to cancer treatment and prevention.[107,108]

Tumor Prevention by Rapalogs

While rapamycin and other rapalogs are modestly-potent anticancer drugs, they are effective cancer-preventive agents. Remarkably, their cancer-preventive effects were initially detected in humans. Patients, who received rapamycin due to renal transplantation, had a peculiar "side effect": a decrease in cancer incidence.[109-114] In cancer-prone mice, rapamycin dramatically delays cancer. For example, rapamycin decreased incidence and progression of tobacco carcinogen-induced lung tumors.[115] Also everolimus (rapalog), delayed tumor onset and progression in a transgenic mouse model of ovarian cancer.[116] Rapamycin inhibited multiple stages of tumor progression in a transgenic mouse model of HER2-positive breast cancer.[117] Rapamycin also prevents skin tumors induced by phorbol esters.[118] It was assumed that rapalogs delay cancer by targeting cancer cells directly. Yet, there were some indications that the effect might be indirect via targeting normal cells. $Lkb1^{(+/-)}$ mice were treated with rapamycin from the age of 8 weeks, well before the onset of polyposis. This decreased the number of gastric tumors. In the polyps from the treated mice, phosphorylation of S6 kinase (a marker of mTOR activity) was maintained.[119] Still, in these studies, the effect of rapamycin on overall longevity and rate of aging was not determined. When the rate of aging was measured, it was revealed that rapamycin at least "formally" decreased the rate of aging and increased maximal longevity in transgenic HER-2/neu cancer-prone mice.[120]

Indirect "Anti-Aging" Model

It was suggested that cancer could be prevented by inhibiting aging with rapamycin or "by staying young."[121] Rapamycin decreased cancer incidence in normal (non-cancer-prone) genetically heterogeneous mice[27,28] and inbred mice.[29] These studies have been initiated in order to evaluate the effect of rapamycin on aging not cancer. Although retrospectively one may argue that life span was extended due to cancer prevention, this argument could (or not) be used to explain the life extending effect of calorie restriction as well. It is clear that dramatic difference in lifespan between man and *C. elegans* is not due cancer, but instead due to the speed of development and aging. Also in order to delay cancer and extend life span in $p53^{+/-}$ mice, treatment with rapamycin should be started earlier in life before tumors develop.[122] Perhaps rapamycin is less effective when cancer had developed already. CR delays cancer in $p53^{-/-}$ mice.[123-125]

How to Distinguish between Two Models of Cancer Prevention

Two models of cancer prevention are very difficult to distinguish. One may believe that rapamycin prolongs life span by decreasing cancer (**Fig. 1A**). Yet, I believe that rapamycin prevents cancer by suppressing aging (**Fig. 1B**). It may be helpful to evaluate rapamycin in strains of mice with low tumor incidences. This might confirm that rapamycin increases life span independently from cancer prevention. In fact, it is already known that rapamycin delays most age-related diseases in rodents,[126,32] including age-related

retinopathy[127] and age-related obesity.[128] Second, we can test the cancer-preventive effect of rapamycin at low doses that do not inhibit cancer cell growth. Other approaches might be suggested by the readers of this paper (please address as letter to the editor).

Rapalogs for Cancer Prevention

For cancer prevention via inhibiting the aging process, rapamycin (and other rapalogs) could be used at lower doses in order to target normal cells, which are very sensitive to rapamycin.[129] There is no need to kill any cells. Furthermore, there is no need to inhibit mTOR completely: it could be inhibited just slightly to slow down aging. Second, administration of rapamycin can be intermittent, like intermittent fasting. In low doses or intermittent schedules, rapalogs may have no side effects. Rapamycin prevents cancer in $p53^{-/+}$ mice, which could be viewed as a model of Li-Fraumeni syndrome. Currently, there is no clinically-available therapy to prevent cancer in patients with Li-Fraumeni syndrome.[130-132] Definitely, there is an excellent opportunity to start cancer prevention by rapalogs.

Selective Protection of Normal Cells from Therapy-Induced Cell Death and Senescence

Numerous studies have demonstrated that rapalogs potentiate chemotherapy against cancer cells. In theory, rapalogs could protect normal cells from chemotherapy and to increase therapeutic index.[63] In cell culture, rapamycin in combination with the p53-inducing agent Nutlin-3 and metformin can selectively protect normal cells from chemotherapy.[133-135] Remarkably, in mice rapamycin prevented epithelial stem cell senescence and protects from radiation-induced mucositis.[136,137] Like rapamycin, fasting inhibits the mTOR pathway. Fasting also increases therapeutic window and decreases side effects chemotherapy in animals and humans.[138-141]

Conclusion

There are several lines of reasoning suggesting that the effects of rapamycin on cancer prevention are indirect. First, while rapalogs (as monotherapy) are relatively modest anticancer drugs, these drugs are potent cancer-preventive and anti-aging agents. Second, typical anticancer drugs do not and cannot be used for cancer prevention. For example, radiation, paclitaxel and doxorubicin, just to mention a few, have no cancer-preventive effects in animals. In contrast, these treatments tend to cause secondary cancer in both animals and humans. Direct anticancer drugs are rather carcinogenic. Third, an anti-aging effect is sufficient to explain cancer-preventive effects. Yet, we might never indisputably distinguish between the anticancer and anti-aging effects of rapamycin because both cancer and aging share the activation of a common signaling pathway, and this pathway is targeted by rapamycin.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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