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Immunosuppressants in cancer prevention and therapy

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Rapalogs such as rapamycin (sirolimus), everolimus, temserolimus, and deforolimus are indicated for the treatment of some malignancies. Rapamycin is the most effective cancer-preventive agent currently known, at least in mice, dramatically delaying carcinogenesis in both normal and cancer-prone murine strains. In addition, rapamycin and everolimus decrease the risk of cancer in patients receiving these drugs in the context of immunosuppressive regimens. In general, the main concern about the use of immunosuppressants in humans is an increased risk of cancer. Given that rapalogs are useful in cancer prevention and therapy, should they be viewed as immunosuppressants or immunostimulators? Or should we reconsider the role of immunity in cancer altogether? In addition to its anti-viral, anti-inflammatory, anti-angiogenic and anti-proliferative effects, rapamycin operates as a gerosuppressant, meaning that it inhibits the cellular conversion to a senescent state (the so-called geroconversion), a fundamental process involved in aging and age-related pathologies including cancer.

Introduction: The Paradox of mTOR Inhibitors

Rapamycin (sirolimus or Rapamune®) and its analogs such as everolimus, temsirolimus (a prodrug of rapamycin) and deforolimus inhibit mechanistic target of rapamycin (MTOR, best known as mammalian target of rapamycin, mTOR). Rapalogs have only one target, the so-called mTOR complex 1 (mTORC1),[1–5] and exert therefore almost identical effects, including an indirect activity on mTORC2 in some models.[6,7] Rapalogs are currently employed in several clinical applications, including cancer therapy and the management of organ transplantation. Actually, these 2 indications appear at odds with each other. The use of rapalogs in organ recipients was indeed justified by their immunosuppressive activity. As such, rapalogs were expected to increase the incidence of cancer and/or to favor tumor progression. Nonetheless, rapalogs are increasingly more used in cancer therapy.[8–18] As a matter of fact, rapamycin and everolimus not only do not increase cancer incidence in transplant recipients but limit oncogenesis in such patients,[19] as we will discuss later. In other words, rapamycin and other rapalogs, which had been initially developed as immunosuppressants, turned out to be cancer-preventive agents. One possible explanation for such a dual activity of rapalogs is that mTOR is frequently hyperactivated in malignant cells.[15–20] But this is only a part of the answer. A second explanation is indeed that rapamycin may prevent cancer by slowing down aging, being cancer an age-associated disease.[21–23]

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Cancer is an Age-Related Disease

The incidence of common cancers including breast, lung, prostate, colorectal, gastric, thyroid, pancreatic, and ovarian carcinomas as well as of some types of leukemia is increased exponentially with age.[21,22] Furthermore, cancer is a leading cause of death "from aging" in most mammals. Thus, any nutritional, pharmacological, or genetic intervention that decelerates aging (for example, caloric restriction) also postpones cancer.[24–29] This predicts that drugs that slow down the aging process delay or prevent oncogenesis.[21] Do such drugs exist? And what are their targets?

mTOR and Geroconversion

Cellular models of accelerated senescence have been useful to define the molecular and cellular bases of aging.[30,31] Cultured cells are generally overstimulated by growth factors, nutrient-rich conditions and elevated oxygen levels. In such conditions, growth-promoting pathways such those mediated by mitogen-activated protein kinases (MAPKs) and the phosphoinositide-3-kinase (PI3K)/mTOR axis are activated. Cells grow therefore in size and then divide. Conversely, various stress conditions can cause an arrest of the cell cycle by promoting the activation of the oncosuppressor p53 and/or the accumulation of cell cycle inhibitors such as cyclin-dependent kinase inhibitor 1A (CDKN1A, best known as p21CIP1) and cyclin-dependent kinase inhibitor 2A (CDKN2A, best known as p16INK4A). When the cell cycle is arrested, cultured cells are still stimulated by growth factors and, in the case of malignant cells, oncogenic signaling pathways. All these factors activate mTOR and MAPK signaling.[32–38] In proliferating cells, mTOR stimulates growth, replication and other cellular functions, for instance, protein synthesis. Conversely, in cells undergoing a cell cycle arrest or in quiescent cells, mTOR

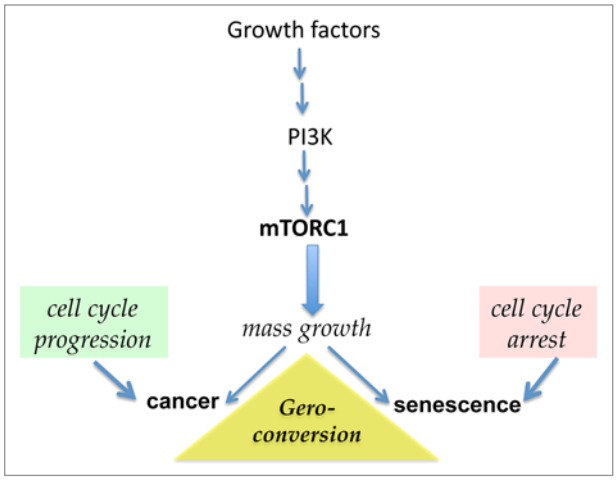

Figure 1. The mTOR pathway is involved in both cancer and senescence. Growth factors, cytokines, insulin, nutrients, and oncoproteins activate the phosphoinositide-3-kinase/mammalian target of rapamycin (PI3K/mTOR) signaling pathway, which promotes cellular growth and cell cycle progression. Mutations that results in constitutive activation of the mTOR pathway are involved in oncogenic transformation when intrinsic controls on cell cycle progression are disabled. Conversely, when mTOR is activated and the cell cycle is arrested, cells enter a senescent state. Rapamycin and other rapalogs (e.g., everolimus) inhibit the mTOR complex 1 (mTORC1) and suppress such a geroconversion.

promotes not only hypertrophy, an hypersecretory phenotype and the hyperactivation of other cellular functions, but also signal resistance, all of which are hallmarks of senescence.[39–42] In these conditions, cells can enter the S phase of the cell cycle but cannot divide, even when they are released from the cell cycle-arresting conditions.[43] Thus, an hypermitogenic drive and the unscheduled entry in the S phase of the cell cycle co-exist with the loss of proliferative and regenerative potential.[43,44] In cells undergoing a cell cycle arrest, mTOR-dependent and mTOR-related signaling pathways drive a conversion to senescence (**Fig. 1**). In culture, a geroconversion usually takes several days, eventually resulting in the permanent acquisition by the cell of a senescent phenotype.[45] Rapamycin and other inhibitors of mTOR decelerate or suppress geroconversion.[45–49] By activating mTOR, the products of multiple oncogenes accelerate geroconversion. In contrast, tumor suppressors, including phosphatase and tensin homolog (PTEN) as well as p53, decelerate geroconversion by inhibiting mTOR.[31,50–56] Therefore, p53 plays a dual role in senescence: it promotes a cell cycle arrest in response to stress but suppresses geroconversion.[57–62] Like other oncosuppressors, p53 may exert anti-aging effects.[63–66] Of note, mTOR is also involved in the geroconversion and exhaustion of quiescent and stem cells in the organism.[67,68] If the mTOR-driven geroconversion constituted a cellular basis of organismal aging, the inhibition of mTOR-dependent signaling pathways would extend lifespan in animals.

TOR Pathways is Involved in Aging

The inhibition of TOR slows aging and prolongs lifespan in diverse species.[69–76] Importantly, rapamycin extends the lifespan of mice.[77–82] Along similar lines, both metformin and caloric restriction, 2 interventions that inhibit mTOR signaling, also prolong the lifespan and postpone oncogenesis in mammals.[83–86] Thus, mTOR is involved in age-related diseases and rapamycin prevents many age-related diseases.[87–98] Do rapalogs prevent cancer in humans?

Rapalogs Decrease the Risk of Developing Cancer in Humans

Organ transplant recipients exhibit an increased incidence of lymphomas, Kaposi's sarcomas as well as of cutaneous and hepatic cancers, at least in part due to the immunosuppression caused by corticosteroids, cyclosporine, azathioprine, and tacrolimus. Of, note, tacrolimus, an inhibitor of calcineurin, should not be confused with rapamycin (sirolimus), as it does not inhibit mTOR. In 1999, the US Food and Drug Administration approved rapamycin for the treatment of organ transplant recipients. It was expected that rapamycin would increase the risk of these individuals to develop cancer. Unexpectedly, rapamycin turned out to limit the incidence of cancers, including lymphoma, among organ transplant recipients.[19,99–103] Actually, rapamycin also cured pre-existing tumors,[104–109] especially cutaneous Kaposi's sarcoma in kidney-transplant recipients.[108] In 2010, US the FDA approved everolimus for the prevention of organ rejection. Like rapamycin, everolimus also appears to limit oncogenesis among organ recipients. Thus, rapalog-containing therapeutic regimens decrease the risk of transplanted patients to develop a skin cancer.[110–112] In line with this notion, switching from calcineurin inhibitors to rapamycin had an antitumor effect in kidney transplant recipients, decreasing the incidence of secondary squamous cell carcinomas. In particular, the number of such carcinomas developing in organ recipients treated with rapamycin was 3.4-fold lower than that arising in control patients (receiving calcineurin inhibitors).[110] Thus, in several studies, the use of rapalogs has been associated with a significant decrease in cancer incidence. Only in a few studies rapalogs have been reported to exert statistically insignificant anticancer effects, in particular among patients bearing multiple pre-existing tumors.[110] This is consistent with an indirect cancer-preventive activity of rapalogs rather than with direct anticancer effects.[21,22] It is important to emphasize that no clinical trial ever attributed to rapalogs a cancer-promoting activity. Thus, the warning that rapalogs might increase cancer incidence is not supported by clinical data.

It should also be noted that clinical trials recruiting transplant organ recipients aimed at comparing rapalog-containing regimens with other immunosuppressive treatment modalities. In such trials, rapamycin or everolimus were given to patients in substitution of immunosuppressants. Thus, it remains to be clearly determined whether rapalogs themselves prevent cancer or it is the withdrawal of conventional immunosuppressants such as cyclosporine and tacrolimus that plays the most critical role cancer-preventive function in this setting. To answer this question rapalogs must be directly compared with placebo or no treatment, an experimental setting that can be easily investigated in mice.

Rapamycin Prevents Cancer in Mice

Rapamycin is extremely effective in the prevention of cancer in animal models.[80,113–127] For example, when initiated 1 week after the administration of tobacco-specific carcinogens, rapamycin decreased tumor multiplicity by 90%, or 10-fold.[115] Along similar lines, rapamycin has been shown to increase the maximum lifespan of cancer-prone mice while slowing down the aging process.[120] In p53-deficient mice, which are prone to develop several tumors as they age, rapamycin extended lifespan by more than 30%.[118] As mentioned above, the cancer-preventive effects of rapamycin may be due to its anti-aging activity.[21,22,128]

Rapalogs as Anticancer Drugs

Rapalogs are increasingly indicated for cancer therapy, in particular for the treatment of mTOR-dependent cancer subtypes.[9–18,129–132] These selective mTORC1 inhibitors are preferentially effective in the context of combinatorial regimens.[133–138] Rapalogs significantly delay cancer progression or prevent cancer relapse in breast cancer patients.[139,140] In addition to targeting cancer cells in a direct fashion, rapalogs exert multiple indirect anticancer effects.[141] For instance, rapamycin inhibits the senescence of stromal cells, which is known to support tumor progression.[142–145] Another promising application of rapamycin is the prevention of the side effects of chemotherapy, part of which originates from the senescence of normal cells (which rapamycin prevents).[141–149] Also, hyperinsulinemia, obesity and cancer are linked through mTOR-regulated processes, suggesting that rapamycin may also be useful for the treatment of cancer-associated metabolic disorders.[150,151]

Does Immunosuppression Play Role in the Cancer-Preventive Activity of Rapalogs?

Immunosuppressive and anti-inflammatory effects are overlapping, and inflammation is well known to fosters both cancer and aging.[121,152–155] Rapalogs could thus be viewed as anti-inflammatory agents, and—at least in theory—one of the mechanisms whereby rapamycin exerts anticancer effects could be its anti-inflammatory activity.

Immunostimulation by Rapalogs

Rapamycin can improve immune responses, especially in old animals.[67,156–160] Moreover, rapamycin enhances the resistance of aged mice to pneumococcal pneumonia via a mechanism that impinges on the inhibition of cellular senescence.[161] Thus, rapamycin exerts both immunosuppressive and immunostimulatory organismal effects. Noteworthy, immunosurveillance systems are set in place to eliminate senescent (pre-malignant) tetraploid cancer cells.[162–165] Therefore, tetraploidy-inducing chemotherapeutic agents (such as paclitaxel) may elicit anticancer responses by re-activating such an immunosurveillance system.[162,163,166] Rapalogs and other inhibitors of mTOR signaling may induce autophagy, which is involved in both cancer and aging.[167–170] Autophagy is expected to boost anticancer immune responses.[171–180] Rapamycin also exerts antiviral effects in humans.[181,182] In particular, rapamycin has been shown to reduce the risk of cytomegalovirus (CMV) infection,[183–185] and to prevent the progression of liver fibrosis caused by the hepatitis C virus.[186] Moreover, rapamycin appears to control, at least in part, HIV-1 and hepatitis C virus replication. Infections from herpes zoster, herpes simplex, and human papillomavirus are common among kidney transplant recipients that are not treated with rapamycin. Along these lines, the shift from calcineurin inhibitors to rapamycin led to a relief from viral cutaneous warts among transplant recipients.[187] Moreover, rapamycin is effective against the Epstein-Barr virus (EBV),[188] it inhibits the proliferation of EBV+ B-cell lymphomas[189] as well as of EBV+ smooth muscle tumors.[190] Since viruses are involved in at least some types of cancer,[191-193] the antiviral activities of rapalogs can contribute to their cancer-preventive effects.

Gerosuppression and Oncosuppression

Aging is the main risk factor for developing cancer and hence anti-aging drugs should exert a cancer-preventive activity. Aging is associated with metabolic, systemic, and microenvironmental changes that promote oncogenesis, a condition that can be named oncophilia. From a cellular perspective, both the oncogenic transformation and the geroconversion involve the activation of the mTOR signaling pathway, which is almost obligatory for tumorigenesis and cell senescence. One of the main differences between malignant and senescent cells is the status of the cell cycle. In cancer, the control of the cell cycle is disabled. According to this perspective, a cancer cell can be seen as a proliferating senescent cell.[31,50] Senescent normal cells simultaneously manifest a proliferative drive (active mTOR and MAPK signaling, overexpression of cyclin D and E) and a loss of proliferative potential.[43,44] Thus, the senescence of normal cells create a selective advantage for cells that lacking a control on their cycle.[194–198] In this context, geroconversion shifts to oncogenic transformation.

Conclusions

Rapamycin and its analogs decrease the risk of organ transplant patients to develop cancer. Rapalogs also prolong the disease-free and overall survival of patients affected by some tumors. Furthermore, rapamycin markedly prevents oncogenesis in both normal and cancer-prone mice. Some important questions remain to be addressed. As we have reviewed here, rapamycin and everolimus decrease cancer incidence among transplant recipients as compared with other treatment modalities (such as calcineurin inhibitors) that by themselves can increase the risk of these individuals of developing tumors. Do rapalogs decrease cancer incidence as compared with placebo or no treatment? Would they decrease the incidence of cancer among immunocompetent individuals? Would they prevent cancer in healthy individuals? Finally, what should be the doses and administration modalities for rapamycin and other rapalogs to prevent cancer without causing side effects. Further studies are required to address these incognita.

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