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Selective anti-cancer agents as anti-aging drugs

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Recent groundbreaking discoveries have revealed that IGF-1, Ras, MEK, AMPK, TSC1/2, FOXO, PI3K, mTOR, S6K, and NFκB are involved in the aging process. This is remarkable because the same signaling molecules, oncoproteins and tumor suppressors, are well-known targets for cancer therapy. Furthermore, anti-cancer drugs aimed at some of these targets have been already developed. This arsenal could be potentially employed for anti-aging interventions (given that similar signaling molecules are involved in both cancer and aging). In cancer, intrinsic and acquired resistance, tumor heterogeneity, adaptation, and genetic instability of cancer cells all hinder cancer-directed therapy. But for anti-aging applications, these hurdles are irrelevant. For example, since anti-aging interventions should be aimed at normal postmitotic cells, no selection for resistance is expected. At low doses, certain agents may decelerate aging and age-related diseases. Importantly, deceleration of aging can in turn postpone cancer, which is an age-related disease.

Introduction

In the last three decades, hundreds of potential cancer-related targets (oncotargets) have been identified and therapeutics developed. Some of these oncotargeted agents have been approved for cancer therapy. The first and still one of the most spectacular examples is imatinib (Gleevec), targeting Bcr-Abl, PDGFR, and c-kit (Ref).[1-5] The clinical use of imatinib revealed limitations of oncotargeted therapy such as selection for resistance,[1,2,6] which is actually predictable on theoretical grounds.[7] Furthermore, the resistance to oncotargeted drugs is often coupled with highly malignant and aggressive cancer behavior.[8,9] This is accompanied by cancer progression. There are several strategies to overcome some of these obstacles[4,10,11] and even to exploit them.[12,13] Here I discuss that oncotargeted drugs can be investigated for the suppression of the aging process (gerosuppression). For example, selective anti-cancer agents prolong lifespan in *Drosophila*.[14] At first glance, this may seem paradoxical, given that (a) classic anti-cancer drugs cause DNA and protein damage and (b) aging is believed to be driven by the accumulation of damage. However, oncotargeted agents do not cause DNA or protein damage but instead inhibit signal transduction. Second, the evidence emerges that aging is not driven by damage but instead is driven by sensing-signaling pathways governing cellular metabolism and growth.[15-17] And these signaling pathways are identical to oncogenic pathways that drive cancer.[18] Oncotargets are involved in cellular geroconversion, organismal longevity, and age-related diseases.

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Cellular Geroconversion

Nutrients, growth factors, inflammatory cytokines, insulin, and other hormones activate the mTOR (mammalian target of rapamycin) pathway.[19-23] When the cell cycle is arrested, then overactivated MAPK and mTOR pathways cause cellular growth in size, leading to a senescent phenotype.[24] The senescent phenotype is characterized by a large, flat cell morphology (hypertrophy), cellular hyperfunctions such as hypersecretion and proinflammation, and an increased lysosomal activity and lipid accumulation.[24-33] Senescent cells have increased levels of cyclin D1. Despite hypermitogenic drive, the replicative (regenerative) potential is low.[24,34] The conversion from quiescence or reversible cell cycle arrest to senescence is called gerogenic conversion (geroconversion).[18,35] Inhibitors of the PI-3K/mTOR pathway suppress geroconversion.[34-42] Thus, overstimulation of quiescent cells drives geroconversion. In the organism, geroconversion is associated with alterations of homeostasis, which accelerate age-related diseases, leading to organismal death.[43-46]

Oncotargets and Longevity

Numerous genes affect aging in yeast, worm, flies, and mammals. Inactivation of Ras, PI-3K, TOR, and S6K increases lifespan. Pro-aging pathways are antagonized by gerosuppressors such as PTEN, AMPK, TSC1/2, sirtuins, and p53, which are also known as tumor suppressors.[47-63] The IGF-1/PI3K/mTOR/S6K pathway is involved in age-related diseases such as atherosclerosis, organ hypertrophy, diabetic complications, and neurodegeneration.[64-72]

Common Targets in Cancer and Aging

Numerous agents targeting mTOR, PI-3K, growth factor receptors, and related tyrosine kinases, Ras, Raf, and B-Raf, S6K, MEK1/2 have been tested to treat cancer.[73-86] The mTOR pathway is almost obligatorily activated in cancer.[18] When the cell cycle is blocked, then mTOR drives geroconversion. When the cell cycle is activated, mTOR drives growth and is involved in malignant phenotype. Therefore, in cancer, the cell cycle control

should be disabled, for example, due to the loss of p53, p16, p27, or Rb. Noteworthy, p53 inhibits both cell cycle progression and the mTOR pathway.[18,36,87-90] Rapalogs (rapamycin and its analogs), which not only inhibit mTOR but also slow down the cell cycle, partially substitute for p53.[18]

Rapalogs

Rapamycin (sirolimus) and their analogs (everolimus, temsirolimus, and deforolimus) bind FKBP12 and thus inhibit mTOR complex 1 (mTORC1).[91-93] Rapalogs are anti-cancer drugs.[20,22,94-103] Rapamycin (sirolimus) and everolimus decrease cancer incidence in renal transplant patients.[104-107]

Temsirolimus and everolimus are approved for the treatment of renal cell carcinoma, breast cancer, progressive neuroendocrine tumors of pancreatic origin, and subependymal giant cell astrocytoma and are investigated for numerous other malignancies.[94-111] In addition, ATP-competitive inhibitors of the TOR kinase undergo clinical trials. Unlike rapalogs, they inhibit both mTOR complex 1 and mTOR complex 2 and also rapamycin-independent functions of mTORC1.[79,112-121]

Akt and PI3K Inhibitors

Knockout of PI3K extends the lifespan of *C. elegans* almost 10-fold.[122] And PI3K is one of the most promising oncotargets[123-131] Mutations in PI3Kα facilitate invasion and metastasis. Small molecule inhibitors of PI3Kα prevented metastasis formation in mice but not xenografts or primary intra-abdominal tumors.[132] Perifosine, an Akt inhibitor, can be safely administered, but it lacks sufficient anti-cancer efficacy in cancer patients.[133-135]

MEK and Raf Inhibitors

Trametinib, an MEK inhibitor, has been approved for treatment of melanoma.[136] Trametinib, as compared with chemotherapy, improved rates of progression-free and overall survival among patients who had metastatic melanoma with a BRAF (V600E or V600K) mutation.[137] MEK inhibitors also undergo numerous clinical trials alone and in combinations. Other MEK inhibitors in clinical development include selumetinib, pimasertib, refametinib, PD-0325901, TAK733, MEK162, RO5126766, WX-554, RO4987655, GDC-0973, and AZD8330.[136,138,139] Also, MEK inhibitors can be combined with oncotargeted agents.[140,141] Resistance and cross-resistance is common[142-144]

Although BRAF and MEK inhibitors have proven clinical benefits in melanoma, most patients develop resistance. Resistance to therapy with BRAF kinase inhibitors is associated with reactivation of the MAPK pathway. Combined treatment with dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, can improve progression-free survival.[145] However, BRAF-inhibitor resistance mechanisms may also confer resistance to MEK-inhibitor and combined therapy.[142,146,147] The resistance may be associated with MAPK and S6 kinase activation. A combination of dabrafenib, trametinib, and the PI3K/mTOR inhibitor GSK2126458 can inhibit tumor growth.[143] It is important to note that monotherapy with RAF inhibitors vemurafenib and sorafenib may cause cutaneous epithelial proliferations (keratosis pilaris, seborrheic keratosis, verruca vulgaris, actinic keratosis, keratoacanthoma, and squamous cell carcinoma).[148] While RAF inhibitors are effective against melanomas with BRAF V600E mutations, they may induce keratoacanthomas and cutaneous squamous cell carcinomas by selecting for RAS-primed cells. Inhibition of MEK together with RAF prevents formation of these tumors.[149] Thus, due to potential selection for Ras-mutant cells, Raf inhibitors unlikely can be used for anti-aging applications.

Cancer Prevention

The suggestion that targeted agents can be used for cancer prevention is not novel. Yet, it was thought that these cancer-specific drugs should target specifically pre-malignant and malignant cells. Here I discuss a very different approach. In theory, certain oncotargeted agents may prevent cancer, if they slow down the aging process and suppress geroconversion. Importantly, such approach does not require targeting malignant cells directly. Chemoprevention due to gerosuppression does not depend on mutational profile of cancer cells or on any features of cancer cells. For example, if rapamycin suppresses aging, it will prevent any cancer including those with p53 and Rb mutations or ErbB activation. In fact, rapamycin prevents cancer in p53-deficient and Rb-deficient mice[150-153] as well as common cancers in normal mice.[154-160] Metformin, which affects the mTOR pathway and slows aging, also prevents a variety of cancers.[161-165] Cellular aging predisposes to cancer[18,166-169] and CR can decrease cellular senescence.

Calorie restriction (CR) decelerates aging. CR delays cancer in humans and other mammals. Anything that decelerates aging (for example calorie restriction and genetic manipulations) also postpones cancer.[170-175] This predicts that drugs that slow down the aging process will delay or prevent cancer.[176]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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