Cancer Prevention Research

Perspective
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Rapamycin and mTORC1 Inhibition in the Mouse: Skin Cancer Prevention

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Abstract

Therapeutic and preventive effects of rapamycin include reduced risk of nonmelanoma skin cancer (NMSC). In this issue of the journal (beginning on page 1011), Checkley and colleagues report that rapamycin inhibits mTOR complex 1 in murine epidermis, thereby inhibiting tumor promotion mediated by tetradecanoyl phorbol-13 acetate in association with a strong anti-inflammatory effect. Rapamycin is an immunosuppressive drug for preventing graft rejection in organ transplant recipients and reduces the risk of NMSC and Kaposi's sarcoma in this population, albeit by mechanisms distinct from immunosuppression. Important future directions include identifying molecular predictors of rapamycin/rapalog sensitivity or resistance (potentially, for example, PI3K pathway alterations and *KRAS* mutations) and combined non-rapalog, mTOR-targeting approaches, all of which should increase efficacy and minimize toxicity. *Cancer Prev Res; 4(7); 957–61. ©2011 AACR.*

The lifetime risk for skin cancer exceeds the lifetime risk of all other cancers combined (1, 2). It is estimated that more than 1.2 million new cases of nonmelanoma skin cancer (NMSC), including squamous cell carcinoma (SCC) and basal cell carcinoma, are diagnosed annually in the United States (1). The risk for NMSC is greatly increased in chronically immune-suppressed organ transplant recipients (3). The molecular mechanisms involved in the pathogenesis of NMSC are not fully understood.

SCC pathogenesis is characterized by the inhibition of apoptosis and enhancement of cell proliferation, resulting in the recruitment of initiated premalignant cells during progression to cancer (4, 5). In murine skin, sustained activation of AKT because of exposure to tumor-promoting agents such as tetradecanoyl phorbol-13 acetate (TPA) and ultraviolet B (UVB) has been shown to cause benign lesions (papillomas), which progress at a certain frequency to SCC. AKT activation is accompanied by increased phosphorylation of its effector molecules including mTOR, glycogen synthase kinase 3 beta (GSK3β), and BAD, suggesting the possibility that AKT and its downstream signaling pathways are involved in skin tumor promotion (6–8). Direct support for AKT involvement comes from studies showing that epidermal overexpression of wild-type AKT or a constitutively active form of AKT (myristoylated-AKT) enhances susceptibility to chemically induced skin cancer (8). A major mechanism by which AKT can augment skin cancer is activation of mTOR, a serine/threonine protein kinase that regulates cell growth and proliferation by enhancing both Cap-dependent and 5′-terminal oligopyrimidine (TOP) mRNA-dependent protein synthesis (9, 10).

mTOR functions intracellularly as a physiologic sensor of nutrients, regulating metabolism and growth (10) and is the catalytic subunit comprising the distinct complexes mTOR complex 1 (mTORC1) and mTORC2. These complexes are distinguished by unique accessory proteins, regulatory associated protein of mTOR (RAPTOR) for mTORC1 and rapamycin-insensitive companion of mTOR (RICTOR) for mTORC2. The two mTOR pathways represent an intricate network with multiple feedback loops. In brief, mTORC1 immediate substrates S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E (elF4E)-binding protein 1 (4E-BP1) associate with mRNA and regulate mRNA translation and initiation, thereby controlling the rate of protein synthesis (10–13). Whereas unphosphorylated 4E-BP1 suppresses mRNA translation, phosphorylated 4E-BP1 (by mTORC1) disassociates from eIF4E and allows it to recruit the translation initiation factor elF4G to the 5′ end of mRNAs. Phosphorylation of S6K1 by mTORC1 promotes mRNA translation and, in turn, phosphorylates or binds multiple proteins including eukaryote elongation factor 2 kinase (eEF2K), S6K1 Aly/REF-like target (SKAR), 80-kDa nuclear cap-binding protein (CBP80), and eIF4B (14). mTORC1 also controls the activity of several transcription factors involved in lipid synthesis and mitochondrial metabolism (10, 15). Dysregulated mTORC1 signaling in humans is associated with the Peutz–Jeghers syndrome (due to LKB1-inactivating mutations) and with colorectal cancers having adenomatous

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doi: 10.1158/1940-6207.CAPR-11-0266

Table 1. Summary of animal studies supporting the role of rapamycin-mediated inhibition of mTOR in cancer therapy/prevention

Cancer type	Description of effects	References
Skin	Reduction in tumor numbers, tumor size, and progression of benign lesions to SCCs in UVB-induced SKH-1 hairless, DMBA–TPA 2-stage and cyclosporine A–mediated carcinogenesis in various murine models	22, 26, 38–41
Head and neck	Reduction in the oral carcinogen-specific mouse model, human xenograft, and oral-specific Kras/p53 two-hit carcinogenesis murine models	22, 42–44
Gastrointestinal (liver, intestine, stomach, and pancreas)	Inhibition of hepatocellular carcinoma in xenograft and orthotopic murine models; reduction in intestinal polyp formation and mortality in ApcΔ716 engineered mice; inhibition of gastric cancer in xenograft immune deficient mouse models; mimicked the anticancer effects of calorie restriction in a murine model of pancreatic cancer	28, 36, 45–47
Kidney	Inhibition of tumor growth in A/J $Tsc2^{+/-}$ mice and xenograft models	48, 49
Breast	Inhibition of tumor growth of premalignant and malignant lesions in ductal carcinoma *in situ* and Erb2-dependent transgenic breast cancer mouse models	50, 51
Prostate	Diminution of prostate adenocarcinoma in $Pten^{+/-}$ and $Pten^{+/-}$/$Tsc2^{+/-}$mice.	52
Bladder	Prevention of invasive bladder cancer in a murine model carrying bladder epithelium-specific deletion of p53 and Pten.	53
Rhabdomyosarcoma	Lack of published studies in murine models, however, a clear benefit of combinatorial chemotherapy in humans	54
Lung	Inhibition of benzo(a)pyrene-, tobacco carcinogen (NNK)-induced lung tumorigenesis in A/J as well as in Tsc1/Kras double-mutant mice	23, 55, 56
Anal	Rapamycin slowed the growth of anal cancer both in a murine model and in humans	57
Uterine	Eker rat model of uterine leiomyomata faithfully recapitulates the human transcriptional profile of this tumor. In this model, mTOR activation (followed by IRS-1 phosphorylation) occurs early, or in endometrial hyperplasia, and the rapamycin analogue WAY-129327 significantly decreased hyperplasia, proliferation, and tumor incidence, multiplicity, and size	58

Abbreviations: DMBA, 7,12-dimethylbenz[α]anthracene; NNK, nicotine-derived nitrosamine ketone; IRS-1, insulin-receptor substrate 1.

polyposis coli (*APC*) loss-of-function mutations (10). Tuberous sclerosis complexes 1 and 2 (TSC1 and TSC2) function as tumor suppressors and are implicated in kidney cancer (9), presumably through their effect on the mTOR signaling pathway. The TSC1–TSC2 complex acts as a GTPase-activating protein. Following phosphorylation by 5′-AMP–activated protein kinase (AMPK), TSC2 stimulates Ras homologue enriched in brain (RHEB), thereby inhibiting mTORC1 signaling. TSC2 also can be phosphorylated by AKT or GSK3β, which negatively regulates mTORC1, providing additional evidence for the existence of multiple regulatory mechanisms of the mTOR signaling pathway and cell growth.

mTORC2 is associated with the regulation of cytoskeletal organization and cell polarization. mTORC2 phosphorylates and activates AKT through a feedback loop [at serine 473 (Ser473)], including serum- and glucocorticoid-regulated kinase and protein kinase C (PKC), thus playing an important role in regulating cell survival, cell-cycle progression, and anabolism. After phosphorylation at Ser478, AKT is primed for further phosphorylation at threonine 308 (Thr308), which leads to its full activation. TPA is a potent inducer of PKC in this context, enhancing phosphorylation of AKT at both Ser473 and Thr308. Rapamycin inhibits mTORC1, but chronic use of this drug may also inhibit mTORC2 (16). Rapamycin binds to a 12-kDa FK506-binding protein, also known as prolyl isomerase (PPIase), thereby inhibiting the ability of mTORC1 to phosphorylate its downstream effectors. mTORC1 inhibition by rapamycin or other rapalogs has antineoplastic effects, suggesting that mTORC1 is a relevant common effector protein complex involved in the pathogenesis of various cancers (Table 1). Specifically, epidermal transgenic expression of RHEB, a direct activator of mTORC1, sensitized murine

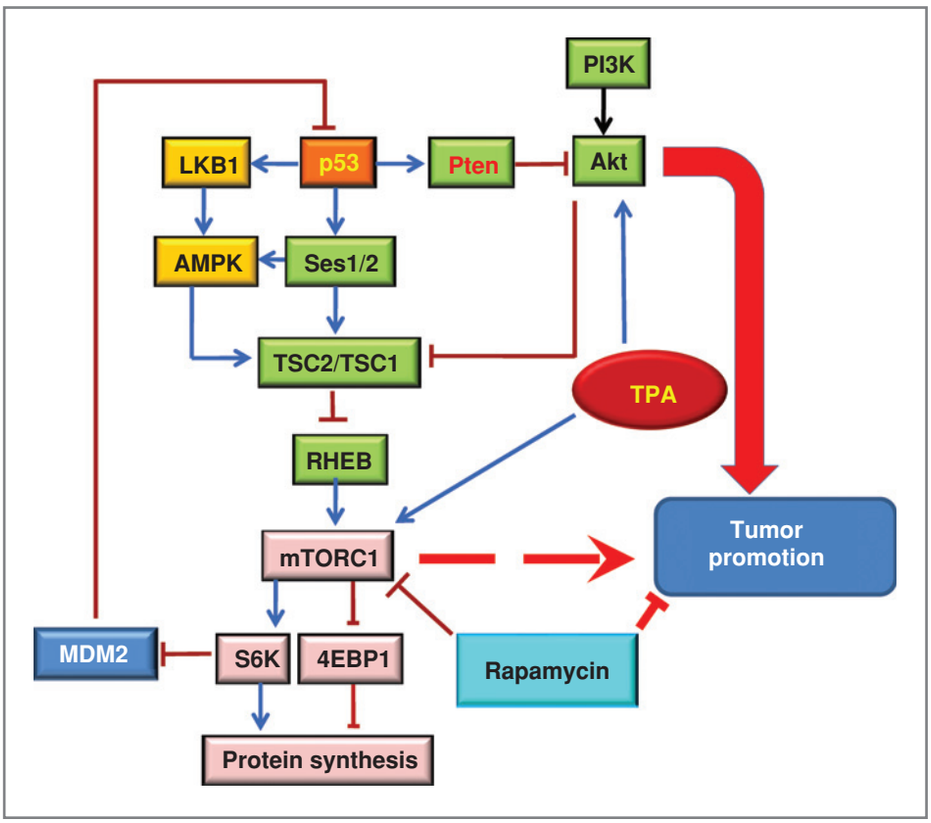

Figure 1. mTOR signaling cascade in the pathogenesis and prevention of skin cancer. The skin tumor promoter TPA induces mTORC1 activity, which in turn enhances the AKT-dependent cell survival signaling pathway. TPA-mediated mTORC1 activation augments epidermal hyperplasia and dermal inflammation. Rapamycin inhibits TPA-mediated inflammation and tumor promotion by inhibiting mTORC1 activity. MDM2, murine double minute 2.

skin to SCC induction (17). The phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathway is also activated by mutations in the p110α submit of *PI3K* called *PI3CA*, and preclinical investigations suggest that *PI3CA* mutations may predict the clinical outcome of PI3K/AKT/mTOR-axis inhibitors (18).

In this issue of the journal, a report by Checkley and colleagues further expands our understanding of the mechanisms by which rapamycin inhibits phorbol ester–mediated skin tumor promotion (19). These investigators showed that the inhibition by rapamycin of TPA-induced mTORC1 [characterized by enhanced phosphorylation of mTOR (Ser2448), p70S6K (Thr389), p4E-BP1 (Ser65 and Thr37/46), pS6-ribosomal protein (Ser240/244), and AKT (Thr308, Ser473)] resulted in a significant reduction in the epidermal labeling index as well as TPA-induced hyperplasia. Of importance, these events were followed by a significant decrease in dermal inflammation that was associated with decreased infiltration of inflammatory cells (T cells, macrophages, neutrophils, and mast cells). Chronic inflammation is a known risk factor for various human cancers, including skin cancer (20). These data suggest that mTORC1 is a key regulator of proliferation and inflammation at the site of TPA treatment of mouse skin. Presumably, therefore, rapamycin inhibits expression of multiple cytokines/chemokines and their receptors, known to promote proliferation and inflammation responses (21). However, the anti-inflammatory effects of rapamycin on macrophage and T-cell infiltration may depend on the type of treatment protocols, including routes of administration (22, 23).

An important finding in this article was that, contrary to its inhibitory effects at lower doses on AKT phosphorylation, rapamycin increased AKT phosphorylation at both Ser473 and Thr308 when given at 200 nmol in multiple administrations. Although the mechanisms for these observations are unclear, the authors suggest that an mTOR-dependent negative feedback loop may be responsible. It is conceivable, however, that the effects of rapamycin on cell-survival signaling are associated with a biphasic dose response which involves distinct mechanisms. A clarification of this as yet unresolved issue would require the demonstration that rapamycin-mediated inhibition of AKT phosphorylation at both Ser473 and Thr308 also occurs through its inhibition of mTORC2 and that rapamycin is able to inhibit TPA-induced PKC (vide supra). Loss of RICTOR results in a complete loss of AKT phosphorylation at Ser473, leading to suppression of phosphorylation of the transcription factors forehead box O 1 (FOXO1) and FOXO3 but not of its other substrate TSC2 (tuberin). Apparently, mTORC2 favors cell survival through AKT-mediated inhibition of FOXO1 and FOXO3, which are known to activate genes that promote apoptosis (10, 20). This year, Zinzalla and colleagues provided evidence that mTORC2 is activated by its direct physical association with the ribosomal machinery which ensures

that mTORC2 activity is calibrated to complement the intrinsic growth capacity of the cell (24, 25).

Of importance, Checkley and colleagues also observed that rapamycin is a potent inhibitor of TPA-mediated tumor promotion in murine skin (Fig. 1). It abrogates papilloma formation and reduces the progression of papillomas to SCC (19). Similar anticarcinogenic effects of rapamycin (Table 1) were previously reported in UVB-induced photocarcinogenesis and 2-stage chemical carcinogenesis murine models (22, 26). Consistent with the observations of Checkley and colleagues, rapamycin has preventive and therapeutic effects on cancer in humans (27–31). A significant clinical effect of rapamycin treatment is its ability to delay the development of premalignancies and to reduce the incidence of new NMSCs in organ transplant recipients (3).

In conclusion, by using the TPA-induced skin cancer model in mice, Checkley and colleagues have provided new insights into the potential utility of rapalogs in preventing and treating environmentally induced skin cancer. Their data indicate that signaling through mTORC1 contributes significantly to inflammation and ultimately to skin tumor promotion (Fig. 1). On the basis of the understanding of compensatory feedback loops between mTORC1 and mTORC2, second-generation inhibitors of this pathway have been developed (32). These agents simultaneously inhibit both mTOR complexes, and some of them also inhibit PI3K, which is a key player in regulating this feedback loop (18). mTOR inhibitors require a word of caution, however: despite their strong effect in preventing cancer in both animals and humans, their chronic use in humans is associated with a number of side effects which often require discontinuation of therapy and are a major concern in the cancer prevention setting (3, 18, 33). Metformin and other biguanides may have a role in addressing this concern. These agents are widely used in treating diabetes, where they have a tolerable risk profile, and recent data suggest that they may be effective cancer chemoprevention agents (34, 35). *In vivo*, metformin downregulates mTORC1 via several potential pathways, including AMPK-dependent and -independent mechanisms (34, 35). Important data show that caloric restriction partially mimics the anticancer effects of rapamycin in a murine model of pancreatic cancer (36). Substantial data on potential predictive markers of mTOR-inhibitor efficacy for cancer therapy and prevention have highlighted the predictive potential of *KRAS* mutations and markers of PI3K/AKT pathway activation (37). Predictive markers and combinations of non-rapalog approaches for targeting mTOR should increase efficacy and minimize toxicity. A specific cancer prevention approach combining metformin and caloric restriction modalities as part of an mTOR-targeted regimen should prove useful, particularly because safety is such a critical factor for chemoprevention trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported in part by 1R01CA138998, R21ES017494, NCI N01-CN-43300 and P30AR050948.

Received March 17, 2011; revised May 9, 2011; accepted May 24, 2011; published online July 6, 2011.

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Cancer Prev Res 2011;4:957-961.