Perspective

Rapamycin for Chemoprevention of Upper Aerodigestive Tract Cancers

Phillip A. Dennis

Tobacco carcinogen exposure is responsible for approximately 30% of all cancer deaths and is the most common cause of malignancies of the upper aerodigestive tract, including lung and head and neck cancers. Tobacco-related cancers are often genetically complex and highly resistant to chemotherapy, which underlies the high mortality rates associated with late stage of diagnosis of these cancers. These poor outcomes, combined with the ability to examine epithelial surfaces of the oral cavity and proximal airways, led to clinical testing of many agents to prevent tobacco-related cancers. Unfortunately, several large, expensive phase III cancer chemoprevention trials in the lung were negative or even harmful (1), and the findings of these trials still reverberate throughout the cancer prevention community. These outcomes helped change the design and emphasis of clinical prevention trials, which now are generally smaller and designed to inhibit molecular targets and/or treat pathologic, preinvasive lesions rather than preventing cancer development in higher-risk populations (2–4). Such changes have placed increasing importance on the identification of relevant molecular targets and the development of mouse models to validate these targets.

In this issue of the journal, Czerninski et al. (5) report a pivotal study of a novel carcinogen-driven murine model of head and neck cancer, in which they identify an important role for the serine/threonine kinase mammalian target of rapamycin (mTOR). mTOR is a critical component of the phosphoinositide 3-kinase/Akt pathway, and its phosphorylation and activation promotes protein translation, cell cycle progression, and cellular survival. Because it is ubiquitously expressed, mTOR is important for tumor cells as well as normal cells such as endothelial cells and lymphocytes. Therefore, mTOR is a critical mediator of many key cancer-related processes including angiogenesis and antitumor immunity, and mTOR inhibition would be expected to have pleiotropic effects against tumor growth. The prototypical mTOR inhibitor is rapamycin (sirolimus). Czerninski et al. add an important chapter to the body of work that has established mechanistic connections between carcinogenesis in the upper aerodigestive tract, mTOR activation, and the cancer-preventive effects of rapamycin.

Tobacco components such as nicotine or the tobacco-specific carcinogen 4-(methylNitrosamino)-1-(3-pyridyl)-1-butanone (NNK) can activate Akt and mTOR in human bronchial or alveolar airway epithelial cells and cause a partially transformed phenotype in vitro (6). In A/J mice, NNK induces a full spectrum of lung lesions including adenocarcinomas, and phenotypic progression of NNK-induced lung lesions correlates with activation of Akt and mTOR but not other Akt substrates (7). Activation of mTOR is critical for NNK-induced tumorigenesis because its inhibition by rapamycin (at trough levels similar to those observed in humans taking rapamycin to prevent rejection of kidney transplants) decreases tumorigenesis by 90% in mice (8). Czerninski et al. produced similar results in their model of 4-nitroquinolone-1 oxide (4-NQO)–induced carcinogenesis. 4-NQO causes DNA adducts and oxidative stress and has been used previously to induce oral or tongue lesions in mice and rats (9–11). These investigators showed that 16 weeks of exposure to 4-NQO caused 100% of C56BL/6 mice to develop lesions in the tongue and oral mucosa. After 4-NQO was stopped, many of these lesions progressed to squamous cell carcinomas. Akt and mTOR were activated in the earliest 4-NQO–induced premalignant lesions. Rapamycin not only prevented the phenotypic progression of these premalignant lesions but also caused regression of established squamous cell carcinoma.

Combined with studies showing that rapamycin or rapamycin analogues can prevent tumor development in genetically engineered mouse models of cancer (including K-Ras–driven lung cancer; refs. 12–15), the studies of Czerninski et al. provide a strong rationale for clinically testing rapamycin in prevention of head and neck cancer. Additional support is provided by the U.S. Food and Drug Administration approval of rapamycin (for indications other than cancer prevention, but nonetheless making it readily available and relatively inexpensive), the ability of rapamycin to be taken orally, and the availability of commercial assays to measure rapamycin levels.

Enthusiasm for translating the results of Czerninski et al. into a clinical trial of rapamycin must be tempered by very important safety and efficacy issues. The two major safety issues are the risk of immunosuppression and risk of feedback activation of Akt that could lead to increased tumorigenesis. Rapamycin is Food and Drug Administration approved as an immunosuppressant to prevent rejection of renal allografts. The Food and Drug Administration has issued a black-box warning about rapamycin, stating that increased risks of infection, lymphoma, and nonmelanoma skin cancers have been observed in renal transplant patients taking the drug.1 All of the renal-transplant patients taking rapamycin, however, were also taking cyclosporine and corticosteroids, raising the possibility that rapamycin may be safe as a single agent. Indeed, no increased incidence of immunosuppression has been observed in multiple trials of single-agent rapamycin or rapamycin

1http://www.fda.gov/cder/foi/label/2004/21083s017,21110s020lbl.pdf
analogues in cancer patients (16, 17) or in a large trial of tuber-
ous sclerosis patients who received single-agent rapamycin for
1 year and had serum drug levels equal to or exceeding those
in transplant patients on rapamycin (18). Furthermore, epide-
miologic data suggest that transplant patients maintained on
rapamycin are at a lower risk of cancer (19).

The second rapamycin safety concern—feedback activation of
Akt and increased tumorigenesis—is based on the ability of
rapamycin to de-repress inhibition of the Akt/mTOR
pathway mediated by constitutive phosphorylation of insulin
receptor substrate 1 by S6 kinase (20) and to increase phos-
phorylation of Akt by TOR complex 2 (21). Either mechanism
could lead to increased phosphorylation of Akt at S473, in-
creased Akt activity, and possible promotion of tumor growth
through propagation of the Akt signal to substrates other than
mTOR. Although such feedback phosphorylation of Akt has
been observed in cancer patients treated with a rapamycin an-
logue (22), it has not been observed in multiple mouse stud-
ies (including those of Czerninski et al.), wherein rapamycin
or rapamycin analogues were administered for prolonged per-
iods (up to 10% of the mouse life span). These long-term ad-
ministration data are consistent with in vitro data showing that
TOR complex 2 is inhibited by prolonged exposure to ra-
pamycin (23).

The principal efficacy issue with rapamycin involves its
pharmacodynamics and tissue penetration. Inhibition of
mTOR is readily detected in peripheral blood, but this effect
does not accurately reflect inhibition of mTOR in tissue
(24, 25). The results of Czerninski et al. support incorporating
the analysis of readily biopsied oral tissues into trials of ra-
pamycin for preventing head and neck cancer, so that potential
correlations between rapamycin levels, mTOR inhibition, and
regression of premalignant lesions can be assessed. It is not
presently clear that the levels of rapamycin required for trans-
plant patients will be required for regression of premalignant
lesions.

Czerninski et al. showed that rapamycin was predominant-
ly cytostatic in oral lesions and that inhibition of mTOR was
associated with decreased staining of bromodeoxyuridine, a
marker of cellular proliferation. Cellular response to rapamy-
 cin, however, is likely to be context dependent. Increased p53
staining with phenotypic progression of oral lesions in this
study could indicate that p53 is mutated by 4-NQO treatment.
Although not addressed, p53 mutations are relevant because
rapamycin may have cytotoxic effects in cells with wild-type
p53 that are exposed to DNA damage (26). Determining
which early molecular changes have potential predictive value
in this model system might help in designing future clinical
trials of rapamycin. It is also unclear from these studies
whether rapamycin exerted antitumor effects through direct
inhibition of other cell types such as endothelial cells or lym-
phocytes. Such tumor cell autonomous effects might be impor-
tant because Wislez et al. (14) previously showed that
modulation of chemokine signaling and macrophage function
was important for inhibition of K-Ras–driven lung tumorigen-
esis by a rapamycin analogue.

The 4-NQO model system offers tremendous opportunities
to answer basic questions about the mechanism of action of
rapamycin as a preventive agent, and data from this system
should be compared with data from other systems such as
 tobacco carcinogen–driven lung tumorigenesis in A/J mice.
These comparisons might identify uniform mechanisms of ac-
tivity of rapamycin that can be validated in clinical trials.
Carefully designed prevention trials of rapamycin could po-
tentially be conducted safely and meet focused end points
such as those identified by Czerninski et al. Smaller, early-
phase trials that establish the safety and efficacy of rapamy-
cin in inhibiting mTOR in epithelial tissues and in regressing
premalignant lesions might prompt investment in larger
phase III prevention trials designed to establish whether
rapamycin can prevent upper aerodigestive tract cancers.
Consequently, we have submitted for approval a protocol
using rapamycin in subjects at high risk to develop lung can-
cer, where the end points will include inhibition of mTOR in
bronchial tissues and peripheral blood, regression of pre-
malignant lesions, and assessment of immune function and
overall safety.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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