Perspective

The Molecular, the Bad, and the Ugly: Preventing Bladder Cancer via mTOR Inhibition

Abstract

This perspective on Seager et al. (beginning on p. 1008) considers an important advance in the effort to control bladder cancer. Frontline therapy for superficial transitional cell carcinoma of the bladder involves instillation of the crude immunomodulatory bacterial extract Bacillus Calmette-Guérin directly into the organ. Seager et al. now show that local administration of a chemical inhibitor of mammalian target of rapamycin strongly suppressed growth in a novel preclinical mouse model that develops carcinoma in situ, a particularly problematic form of transitional cell carcinoma of the bladder. The results not only support the clinical evaluation of mammalian target of rapamycin inhibitors in this setting, they open the door for the evaluation of additional molecular local therapies as well.

It is well established that bladder cancer develops along two major molecular tracks (1). The first track is characterized by the development of papillary lesions that rarely become invasive or metastatic but almost always recur (1). These “superficial” tumors are therefore rarely lethal, but their high recurrence rates coupled with patient longevity make them the most expensive solid tumors to treat and therefore a significant public health burden. Superficial tumors are thought to be driven by Ras pathway activation (2), most often (in up to 65% of cases) via the accumulation of activating mutations in the type 3 fibroblast growth factor receptor (3) and less often via mutations in phosphoinositide 3-kinase (4) or Ras itself. The second progression track involves the inactivation of major tumor suppressors [p53, Rb, and phosphatase and tensin homologue (PTEN); refs. 1, 4, 5], and it produces tumors that are highly invasive and metastatic. Although ~50% of these muscle-invasive tumors respond well to cisplatin-based regimens and leads to rapid mortality, superficial tumors are therefore rarely lethal, but their high recurrence rates coupled with patient longevity make them the most expensive solid tumors to treat and therefore a significant public health burden. Superficial tumors are thought to be driven by Ras pathway activation (2), most often (in up to 65% of cases) via the accumulation of activating mutations in the type 3 fibroblast growth factor receptor (3) and less often via mutations in phosphoinositide 3-kinase (4) or Ras itself. The second progression track involves the inactivation of major tumor suppressors [p53, Rb, and phosphatase and tensin homologue (PTEN); refs. 1, 4, 5], and it produces tumors that are highly invasive and metastatic. Although ~50% of these muscle-invasive tumors respond well to cisplatin-based therapies (6, 7), the other half is highly refractory to all current regimens and leads to rapid mortality.

Although superficial and muscle-invasive bladder cancers are considered distinct diseases, there is a form of superficial (non–malignant invasive) cancer, which is called carcinoma in situ (CIS), that often does appear to progress to muscle-invasive disease (8). This form of bladder cancer is characterized by the presence of flat, dysplastic lesions that can involve the whole bladder mucosa via the “field effect.” Current frontline therapy for CIS involves intravesical therapy with the immunomodulator Bacillus Calmette-Guérin (BCG), which produces responses in a majority of patients (9). However, BCG has significant negative side effects, responsive patients recur at a high rate, and there are no effective treatment options for patients who develop BCG-refractory disease. Therefore, it would be of great value to identify less toxic, effective strategies to prevent CIS progression.

Abate-Shen’s laboratory recently showed that nearly 100% of 6- to 8-week-old animals undergoing conditional inactivation of p53 and PTEN via adenoviral Cre delivery to the urothelium develop muscle-invasive tumors by the time they reach 6 months of age (10). Of interest, at earlier time points, these animals develop flat dysplastic lesions characteristic of CIS and display elevated activation of the PTEN/AKT pathway and of the downstream pathway target mTOR (mammalian target of rapamycin; ref. 10). Therefore, and as reported in this issue of the journal, the Abate-Shen group (Seager et al.) evaluated local versus systemic delivery of rapamycin, an inhibitor of the TOR complex 1/mTOR complex, for effects on the progression of CIS lesions in their mouse model (11). Their results indicate that mTOR inhibition produces striking inhibitory effects on tumor progression. More important, local delivery of rapamycin (via intravesical administration) was significantly more effective than systemic administration in blocking the growth of CIS lesions and had very modest to undetectable effects on mTOR pathway activity in peripheral tissues (liver and pancreas).

Limiting systemic exposure to an mTOR inhibitor via an effective local delivery approach is very attractive because the mTOR pathway is centrally involved in metabolism, protein synthesis, and autophagy (12). Several issues are raised by the current study, however. First and foremost, it will be important to determine whether mTOR inhibition causes cell death or merely cell cycle arrest in CIS lesions. If mTOR inhibition does not kill cells, the inhibitor would have to be delivered repeatedly, possibly for the lifetime of the patient, and...
local intravesical delivery, although attractive from a toxicity perspective, is less convenient and comfortable and more costly than a pill. Furthermore, a pill would not be affected by the glycosaminoglycan layer of the bladder mucosa, which presents a physical penetration barrier to intravesical delivery. If an inhibitor is reversible in causing either cell death or cell cycle arrest, steps must be taken to ensure that the drug is present long enough to produce commitment to apoptosis or senescence.

Second, it is not clear that all CIS lesions in patients are equally sensitive to PTEN/mTOR pathway disruption. The preclinical studies in the Abate-Shen groups’ mouse model suggest that tumors with low PTEN expression might be particularly sensitive, and recent work by the Knowles laboratory showing the presence of tuberous sclerosis protein 1 mutations in a significant subset of tumors also could prove to be relevant to sensitivity (13). It probably will be necessary (a) to develop markers of mTOR pathway dependency to identify patients who would benefit most from this approach, and (b) to define the molecular mechanisms underlying the resistance that emerges during prolonged exposure to a pathway antagonist to maximize benefit in initially sensitive patients. As Seager et al. acknowledge, broad assumptions are made when mouse studies are extrapolated to sporadic human tumors because the molecular origins of mouse models are homogeneous and, in this case, linked directly to the pathway under investigation. If type 3 fibroblast growth factor receptor mutations are found to be common in CIS lesions, then another attractive approach for bladder CIS would be to test intravesical delivery of a small molecule type 3 fibroblast growth factor receptor–selective inhibitor.

Last, a top priority for future investigations will be to identify molecular markers that distinguish “benign” from “high-risk” noninvasive bladder cancers. Data of the Abate-Shen group reported in this issue of the journal strongly suggest that PTEN/mTOR pathway activation is one feature that could be used to inform this classification, but a deeper understanding of the molecular mechanisms involved in promoting invasion and metastasis in bladder cancer will undoubtedly produce other features. Our own work indicates that the developmental process of epithelial-to-mesenchymal transition is centrally involved, and we are currently characterizing the expression of epithelial-to-mesenchymal transition markers in CIS lesions and other bladder cancer subtypes associated with a poor prognosis to determine whether these markers can help guide treatment planning.

The study of Seager et al. also underscores the important opportunity to use intravesical administration as an alternative to systemic therapy in bladder cancer patients. Intravesical administration limits the exposure of peripheral tissues to the potentially toxic effects of even the most innocuous investigational agents. The case of intravesical BCG underscores the value of such an approach because systemic BCG exposure produces acute inflammation and sepsis. The authors’ contention that their study is the first to show that intravesical administration of an agent that targets a specific biological pathway can have strongly beneficial chemopreventive effects in a relevant murine model is correct. However, their work expands upon a broad base of studies by other investigators showing that local delivery of immunomodulators (including adenoviral gene therapy; ref. 14) and high-dose conventional chemotherapy can have remarkably beneficial therapeutic effects. By combining molecular profiling with local therapy, we hope that one day soon, bladder cancer will rank among the first human tumors to be effectively prevented and/or treated by “personalized” medicine.

Disclosure of Potential Conflicts of Interest


References

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