USP2a Activation of MYC in Prostate Cancer

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Summary: Ubiquitin-specific protease 2a, a deubiquitinating enzyme, elevates MYC levels in prostate cancer cells via its stabilization of MDM2, undermining p53 regulation of microRNAs that target MYC mRNA. Cancer Discovery. 2(3):206–7. ©2012 AACR.

Commentary on Benassi et al., p. 236 (3).

Inappropriate expression and excess activity of MYC contributes to the development of many human cancers. For human prostate cancer, elevated levels of MYC, accompanied by epigenetic gene silencing and telomere shortening, constitute the earliest and most common molecular events in disease pathogenesis (1). The phenotypic consequences of MYC action in prostate cancer cells include induction of cell proliferation, activation of ribosome biosynthesis and enlargement of the nucleolus, and modulation of cellular metabolism; forced overexpression of MYC in the mouse prostate essentially phenocopies early invasive human prostate cancer (2). Yet, the mechanisms by which MYC becomes dysregulated, and by which prostate cells tolerate MYC-driven transformation, have remained elusive.

In this issue of Cancer Discovery, Benassi and colleagues (3) report a new pathway contributing to MYC action in prostate cancer cells that involves the deubiquitinating enzyme ubiquitin-specific protease 2a (USP2a), p53 and MDM2, and MYC mRNA-targeting microRNAs. MDM2 is known to regulate p53 function both directly, by binding to the p53 N-terminal region to interfere with transcriptional transregulation, and indirectly, through an E3 ligase activity that promotes p53 ubiquitination and proteasomal degradation (4). Previously, USP2a has been found to affect MDM2–p53 interactions by selectively binding and deubiquitinating MDM2, but not p53, resulting in an accumulation of MDM2 in cells and p53 degradation (5).

In these earlier studies, 2 interaction sites in USP2a for MDM2 were discriminated, one at the C-terminus and one at the N-terminus, and USP2a enzymatic activity was needed for its effects on MDM2 because a catalytically dead mutant of USP2a (H549A) failed to augment MDM2 levels (5). Overexpression of USP2a was detected in as many as one-half of prostate cancer cases; by deubiquitinating MDM2 to abrogate p53 function, USP2a was thought to contribute to a neoplastic prostate cell phenotype via undermining the activation of protein-coding genes, such as those regulating cell-cycle checkpoints and apoptosis, which are known transcriptional targets of p53 (6, 7).

The new data collected by Benassi and colleagues (3) now also implicate USP2a in the dysregulation of MYC in prostate cells, a phenomenon attributable to its undermining of the expression of microRNAs that are targets of p53. When forced overexpression of USP2a in immortalized prostate epithelial cells and in LNCaP prostate cancer cells was used, a consistent increase in MYC protein levels was evident, resulting from repression of microRNAs, including miR-34b/c, miR-98, and let-7c, which target the 3’untranslated region of MYC mRNA. The microRNA repression was accomplished by USP2a via its binding and stabilization of MDM2, which acted to prevent p53-mediated transcriptional transactivation of the promoters driving microRNA production. siRNA-mediated knockdown of MDM2 or the administration of Nutlin, which led to p53 activation of miR-34b/c expression, triggered reductions in MYC levels.

The recognition that USP2a–MDM2 interactions can undermine the control of MYC levels by p53-mediated transcriptional regulation of microRNA precursors has broad implications for understanding how MYC activity becomes unleashed in prostate cancer cells and for considering how the dysregulation of MYC might be antagonized therapeutically. In normal prostate epithelial cells, MYC expression appears correlated with proliferative activity (1). However, in prostatic intraepithelial neoplasia (PIN) lesions and in prostate cancers, elevations in MYC protein levels out of proportion to cell proliferation are consistently evident (1). Attempts to ascribe these MYC increases to somatic gains of 8q24, containing the MYC gene, or to frank MYC amplification have been unsatisfying. Although these copy number increases have been reported in aggressive and advanced cases of prostate cancer, the alterations correlate poorly with MYC mRNA and MYC protein expression (1). An inverse correlation between FOXP3 and MYC expression in many prostate cancer cases may be more tantalizing. Reduction of FOXP3 in human prostate epithelial cells by the use of siRNA against FOXP3 mRNA elevates MYC mRNA and MYC protein levels, and targeted deletion of FoxP3 in mouse prostate epithelial cells triggers PIN and similar MYC increases (8). Somatic FOXP3 deletions and mutations have been detected in a fraction of human prostate cancer cases, and reduced FOXP3 expression has been found in others, but whether these changes can explain all of the MYC increases in prostate cancer is not clear (1, 8).
With overexpression of USP2a also evident in a subset of prostate cancer cases, especially those with increases in fatty acid synthase, a protein that, like MDM2, has been reported to be stabilized via USP2a catalytic activity, the consistently high MYC levels in prostate cancers may be a result of more than one mechanism (6). Also, the mechanistic basis for high-level MYC expression in life-threatening metastatic prostate cancer may evolve because MYC amplification has been observed more commonly during the late stages of prostate cancer progression rather than early (1). Further analyses will be needed to ascertain whether USP2a-MDM2 interactions, FOXp3 loss, and MYC copy number changes define mechanistically distinct or clinically relevant disease subsets for prostate cancer or whether these different perturbations in MYC regulation collaborate to drive MYC overexpression. In mouse models, higher levels of MYC expression lead to more aggressive prostate cancer phenotypes (2).

The pathophysiologic upregulation of MYC expression in prostate cancer cells attributable to USP2a catalysis presents a tantalizing opportunity for therapeutic intervention. The transcriptional transactivation properties of MYC have been difficult to antagonize with small-molecule drugs. However, in their studies, Benassi and colleagues (3) found that the MDM2 antagonist Nutlin was able to lower MYC levels in prostate cancer cells, hinting that interruption of molecular pathways upstream of MYC overexpression might be effective at attenuating the MYC contributions to the neoplastic phenotype of at least a subset of human prostate cancers. A variety of agents targeting the p53 pathway are moving toward cancer clinical trials, including more than one small-molecule MDM2 antagonist (9). More importantly, the findings of Benassi and colleagues (3) directly nominate USP2a, and its catalytic activity, as a candidate molecular target for inhibition in the treatment of prostate cancer as well. Presumably, USP2a inhibition, which would not only reduce MYC levels but also activate p53 signaling pathways, might render prostate cancer cells more sensitive to agents such as docetaxel and ionizing radiation, which already are used in the treatment of prostate cancer. Of course, if USP2a’s corruption of MYC regulation accounts for only a subset of prostate cancer cases, attempts at targeting its catalytic activity would only benefit this subtype of the disease.

The selective deubiquitination of MDM2 by USP2a promotes p53 degradation in prostate cancer cells, resulting in a reduction of expression of microRNAs targeting MYC mRNA. The consequence, in the subset of prostate cancer cases with high-level USP2a expression, is overexpression of MYC, a master regulator of the neoplastic phenotype in human prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES
