A Novel Application for Murine Double Minute 2 Antagonists

The p53 Tumor Suppressor Network Also Controls Angiogenesis

Bernd R. Binder

Impairment of the p53 tumor suppressor network\(^1\) is thought to be involved in a large percentage of tumors either by mutations in the p53 gene\(^2\)–\(^4\) or by increased expression of its major control system, the MDM2\(^5\) (murine double minute 2; HDM2 for its human equivalent). It is important to realize that levels of p53 are subjected to an autoregulatory feedback loop by MDM2\(^6\)–\(^7\) as p53 upregulates MDM2 expression and MDM2 protein in turn binds to p53. MDM2 is an E3 ubiquitin ligase and transports p53 to the cytoplasm where it promotes p53 ubiquitination and degradation by the proteasome. In human cancer, increased levels of MDM2\(^6\) are caused either by gene amplification, increased expression induced by activated p53, stabilization by an aberrantly spliced form of HMDX\(^8\), or augmented translation. In addition to these mechanisms, functional single-nucleotide polymorphisms (SNP) such as the 1 at nucleotide 309 (SNP309) in the MDM2 gene can modulate MDM2 expression and cause increased tumor progression.\(^9\)

Thus, mutations in the p53 gene or an increase in MDM2 protein impair the effectiveness of p53-dependent proapoptotic and cell-cycle arrest mechanisms and thereby favor the development of tumors. In addition, MDM2 has also p53-independent activities\(^10\)–\(^11\) through interactions with proteins involved in controlling cell proliferation and survival. This concatenation of data indicated that disruption of the p53–MDM2 autoregulatory feedback loop as well as inhibition of MDM2 would be a suitable strategy for tumor therapy. In fact, Vassilev et al\(^12\) recently developed a class of small molecules, the nutlins (eg, nutlin-3, a tetra-substituted imidazoline), that occupy the p53-binding pocket in MDM2\(^13\) thereby preventing MDM2 binding to p53. Similarly, nutlin-3 also binds to and interferes with MDMX,\(^14\) another component of the p53 tumor surveillance pathway. This leads to a disruption of the autoregulatory feedback loop and consequently the p53 tumor suppressor network is fostered. Consistently, Vassilev et al further showed that nutlin-3 induces apoptosis especially in cancer cell lines with increased MDM2 expression\(^15\) which correlates well with in vivo antitumor efficacy of nutlin-3 (Figure 1).

An antitumor strategy that interferes with the p53 – MDM2 feedback loop should therefore work best in tumors with wild type p53 (approximately \(\approx50\%\) of all tumors) and increased MDM2 which suppresses functional active p53. On the other hand, such a strategy does not appear to be promising in tumors with a mutated p53 gene. In this issue of Circulation Research, Secchiero et al\(^16\) however, report that nutlin-3 may have additional potent antitumor activities by a novel effect of this molecule on angiogenesis. This antiangiogenic effect of nutlin-3 might be an important widening of the possible therapeutic window for nutlin-3 as it is assumed that endothelial cells of blood vessels supplying even a tumor with mutations in p53 do in general not contain such p53 mutations. It is now clear that tumor growth and progression critically depend on an adequate blood supply.\(^17\)–\(^18\) Moreover, antiangiogenic therapies have the advantage of not inducing tumor resistance. Thus, a nutlin-3 based antitumor therapy might also have potential in tumors containing a mutated and nonfunctioning p53 gene.

What are the underlying mechanisms for the antiangiogenic activity of nutlin-3? In this article the authors demonstrate that nutlin-3 has antiangiogenic activities via 3 different mechanisms: (1) by inhibiting endothelial cell migration, which seems to be the predominant effect; (2) by inducing cell cycle arrest; and (3) by increasing apoptotic tendency in endothelial cells. The authors also show that nutlin-3 treatment of endothelial cells leads to accumulation of p53, indicating that the effects of nutlin-3 in these cells are also related to its interference with the p53–MDM2 autoregulatory feedback loop (Figure 2). There are only few reports of a direct effect of p53 in endothelial cells.\(^19\) However, with respect to tumor cell migration an effect of p53 on cell

**Figure 1.** The p53–MDM2 autoregulatory feedback loop in cancer (modified according to Harris\(^24\)): nutlin-3 inhibits increased MDM2 activity and thereby restores p53 levels.
motility has been demonstrated which is largely mediated through the regulation of Rho signaling, thereby controlling actin cytoskeletal organization (reviewed in20). One could speculate that in analogy to tumor cells a similar mechanism might be responsible for the effects in endothelial cells.

The data presented here by Secchiero et al are far from clinical applications and even the in vivo data are restricted to a Matrigel plug system in mice. Nevertheless, these data might open a new route for a broader application of nutlin-3 or other MDM2 antagonists7,21,22 not only for direct antitumor therapies but also for application in antiangiogenic regimens.23

Source of Funding
Supported partially by the EU 6th framework program EVGN (contract number LSHM-CT-2003–503254) and the EU 6th Framework Integrated Project Cancerdegradome (LSHC-CT-2003–503297).

Disclosures
None.

References

Key Words: angiogenesis • MDM2 • p53 • nutlin-3
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*Circ Res.* 2007;100:13-14
doi: 10.1161/01.RES.0000255897.84337.38
*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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