Hypoxia-Inducible Factor-1 and p53: Friends, Acquaintances, or Strangers?

Commentary on Sumiyoshi et al., p. 5112

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In this issue of Clinical Cancer Research, Sumiyoshi et al. (1) report on overexpression of hypoxia-inducible factor-1α (HIF-1α) and p53. HIF-1α and p53 are two of the most highly studied transcription factors; therefore, it is perhaps not surprising that reports of interactions between them abound and are, in turn, the source of much controversy. In brief, both factors are maintained at low or undetectable levels within nonstressed cells but are rapidly stabilized as a result of post-translational modifications, hydroxylation of HIF-1α, and phosphorylation of p53. In both cases, the post-translational modifications cause a subsequent failure to interact with their respective E3 ligases (reviewed in refs. 2, 3). HIF-1α, which is composed of two subunits (HIF-1αa and HIF-1β), is stabilized specifically in response to low oxygen levels, whereas p53 is stabilized in response to a variety of stresses, most notably DNA damage but also hypoxia. In response to hypoxia, p53 has been shown to induce apoptosis through a mechanism seemingly distinct from DNA damage–induced apoptosis (4). The potential mechanisms by which p53 induces apoptosis and tumor suppression in response to hypoxia have been reviewed elsewhere and will not be considered here (5). In contrast, HIF-1α has been implicated as having a role in both cell survival and apoptosis. HIF-1α and its downstream targets (e.g., CAIX) have been used as markers of tumor hypoxia and are known independent prognostic factors for a wide range of tumor types (6). Determining the relative hypoxic fraction of a solid tumor is of clinical relevance, as many studies have shown that the greater the hypoxic fraction, the worse the prognosis for the patient (7–10). The reasons behind this are multifaceted but, for simplicity, can be divided into two categories. Firstly, cells that adapt to a hypoxic environment have a growth advantage and are therefore more aggressive. Secondly, hypoxic cells are more resistant to both chemotherapy and radiotherapy. In their recent study, Sumiyoshi et al. set out to determine what the clinical prognosis was for patients with gastric tumors that stained positively for both HIF-1α and p53. The expression levels of both HIF-1α and p53 were determined by immunohistochemistry in 216 human primary gastric tumors. After significant analysis, Sumiyoshi et al. concluded that HIF-1α expression alone can be used as an independent prognostic marker for gastric tumors but that the combination of HIF-1α and p53 overexpression leads to a more dismal prognosis. Sumiyoshi et al. identified 102 of the 216 (47.2%) gastric tumors studied as staining positive for p53. However, what is most intriguing is whether p53 in this study is wild-type, mutant, or a mixture of both. The N-terminal p53 antibody (1801) used in the study does not reliably distinguish between wild-type and mutant p53. All the tumors examined have regions of hypoxia as indicated by their size and the presence of HIF-1α staining. As previously mentioned, hypoxia induces the accumulation of p53 protein as do oncogenic signals in general. Therefore, it is probable that the p53 staining observed resulted initially as part of the cellular response to hypoxia or oncogenic stress. Of course, as Sumiyoshi et al. point out, if the p53 is wild-type it would be expected to lead to apoptosis and therefore impede tumor progression. A strong selective pressure has been shown to exist within tumors for the mutation or loss of p53 (11). Mutations in p53 occur in upwards of 50% of human tumors, including gastric tumors (12). These mutations in the great majority of cases tend to cluster in the core domain of p53, which is required for DNA binding and transcriptional regulation. Once mutated and unable to effectively transactivate downstream targets, p53 not only is functionally compromised but also evades degradation by the proteosome. The E3 ligase for p53 (MDM2) is a transcriptional target of p53. Therefore, a negative autoregulatory loop exists, whereby in the presence of p53 MDM2 levels increase and p53 is degraded. In contrast, mutant p53 is not able to transactivate MDM2 and so the p53 protein accumulates. In cases where wild-type p53 remains, mutations are often found in the same pathway (e.g., in the Chk2 kinase), which phosphorylates p53 (13–15). The straightforward explanation behind the findings of Sumiyoshi et al. and others is, therefore, that during tumor development loss of p53 was actively selected for and that mutant p53 is what is observed in the tumor sections examined (Fig. 1). These findings, although of great therapeutic significance, only fuel the continuing debate over the relationship between HIF-1α and p53. The data linking p53 and HIF-1α have been reviewed at length and cannot be considered here in their entirety (16). In brief, HIF-1α has been described as mediating the accumulation of p53 in response to hypoxia as well as there being a role for p53 in inhibiting HIF-1α stabilization (17–21). More recently, elegant experiments from Fersht et al. showed that p53 and HIF-1 allele directly via the oxygen-dependent degradation domain of HIF-1α in vitro (22, 23). They showed that HIF-1α exists as an unfolded protein and, because of this feature, resembles DNA. They go on to speculate that it is as a result of this conformation that the DNA binding or core domain of p53 recognizes and binds to the oxygen-dependent degradation domain region of HIF-1α. This theory fits with the
finding that hypoxia-induced p53 does not transactivate its usual target genes (i.e., the p53 present in hypoxic cells is mopped up by HIF-1α and therefore does not transactivate). However, recent data show that, although hypoxia-induced p53 does not transactivate known target genes, such as Apaf-1 or Perp, it binds to the promoters of these genes. Although the data from Fersht et al. effectively show that specific regions of HIF-1α and p53 can interact, they do not address the in vivo scenario. When considering the interaction between HIF-1 and p53, a major conceptual problem is the data, indicating that the two proteins are not stabilized under the same hypoxic conditions. Tumor hypoxia represents a broad range of oxygen conditions ranging from normal physiologic levels to near anoxia. HIF-1 can be stabilized at relatively high levels of oxygen and is certainly seen at 2% oxygen in most cell types studied. In contrast, p53 does not accumulate until oxygen levels decrease to near anoxic levels (e.g., 0.02% O₂). A mechanism by which HIF-1α modulates p53 stabilization therefore requires an anoxic-specific factor, which, although alluded to, has not been identified.

When considering the biological implications of a potential interaction between p53 and HIF-1, it is important to remember that evolution does not put mechanisms in place to deal with tumors. Any interaction between HIF-1 and p53 must therefore have an evolutionary benefit to cells in a hypoxia environment under relevant conditions. This is probably restricted to either development and/or wound healing. HIF-1 is an essential protein during development whereas p53 is dispensable, although p53-null animals develop tumors at an increased rate (24, 25). Mice lacking p53 do not have any evidence of increased or decreased levels of angiogenesis as might be expected if they were unable to modulate an effective response to hypoxia. The same can be said for mice lacking both MDM2 and p53. Since its initial characterization, p53 has been found to represent a family of proteins and is now known to be related to both p63 and p73. The p63 protein certainly has an important role to play in many aspects of normal development and, particularly, of the skin (26). Perhaps, we should consider that HIF-1 and p53 can interact because there is a stronger interaction between HIF-1 and p63. To our knowledge, there is little or no data available on the p63 response to hypoxia.

To conclude, overexpression of HIF-1 negatively influences patient prognosis in part because it is indicative of a significant level of tumor hypoxia. The presence of hypoxic regions within tumors not only induces an adaptive response within the tumor cells so that they overcome otherwise restrictive conditions but also makes standard therapy less efficient. HIF-1 is the principal transcription factor involved in the hypoxic response and is responsible for, among other things, inducing angiogenesis and glycolytic metabolism. Therefore, cells survive and proliferate and tumor development proceeds. The wild-type p53 protein is referred to as having a guardian-like role because it is responsible for monitoring the cellular state and responding to stress by inducing either a cell cycle arrest or apoptosis. During tumor development, p53 can be stabilized by oncoproteins, nutrient depletion, acidosis, and hypoxia or most likely a combination of stresses. When p53 function is lost, the cell therefore looses an efficient gatekeeper, allowing tumor cells to proliferate unchecked. For these reasons, overexpression of
either HIF-1 or p53 negatively affects patient prognosis, so it is perhaps not surprising that having both makes things even more dismal. What remains to be seen is where these findings will lead cancer therapy. For many years now, significant effort has been put into the search for small molecules to restore a functional p53 pathway in human tumors. More recently, there have also been exciting developments in the search for efficacious HIF-1 inhibitors. Targeting HIF-1 and/or p53 therefore represents novel and promising targets for the treatment of all solid tumors.

References

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