INTRODUCTION

The short history of p53 contains an overwhelming number of facts and hypotheses, presenting the challenge of integrating diverse and sometimes mutually exclusive ideas into a coherent picture. It is important to make a distinction between p53 tumor suppressor activity, the mechanism of which remains speculative, and p53 responses to DNA damage, which are well characterized. Because critical steps in tumorigenesis involve genomic fixation of DNA damage-induced mutations, it seems reasonable to assume that DNA damage signaling to p53 would activate p53 tumor suppressor activity. However, this has not been demonstrated, and p53 tumor suppressor activity may not require the acute p53 response to DNA damage (Komarov et al., 1999). Nonetheless, the genotoxic chemicals and ionizing radiation that are clinically used to treat human cancer indisputably activate wild type p53.

DNA damage refers to alterations in the chemical bonds of constituent nucleotides, resulting in aberrant or mismatched base pairs, cross-linked bases, or single- and double-strand breaks in the phosphodiester DNA backbone. DNA damage can be induced by genotoxic chemicals, ultraviolet radiation, shortened telomeres, or reactive oxygen species generated by processes including mitochondrial respiration, ionizing radiation, or ischemia-reperfusion (Giaccia and Kastan, 1998). DNA damage can also be induced by oncogenic alterations in cancer cells, such as...
overexpressed/amplified c-myc, which has been reported to generate excess reactive oxygen species and damages DNA (Vafa et al., 2002).

There is an ongoing “background” of oxidative damage that is continuously repaired (Friedberg, 2003), and this does not detectably activate the p53 DNA damage response. Otherwise, since the p53 response can last for hours to days, p53 would be constantly activated. Thus, when we refer to DNA damage signaling to p53 we refer to a level of damage that is sufficiently above background to result in experimentally detectable changes in p53.

We will focus on how DNA damage signals to p53 and how DNA damage signaling regulates p53 function. Careful consideration of these events casts doubt on the pervasive assumption that post-translational modification of p53 is primarily responsible for DNA damage-induced p53 stabilization.

DNA DAMAGE DETECTION

Conceptually, p53 could be a direct sensor of DNA damage by binding directly to damaged DNA or to DNA damage repair products. *In vitro* p53 can directly bind to irradiated DNA, to DNA which has a short mismatch, or to DNA ends (Lee et al., 1995), (Reed et al., 1995), (Bakalkin et al., 1994). Binding to damaged DNA could be involved in the actual process of DNA repair (Offer et al., 1999) (Zhou et al., 2001) (Rubbi and Milner, 2003b). That lower organisms such as bacteria and yeast lack p53 but possess robust DNA repair systems indicates that p53 is dispensable for DNA repair. Nonetheless, a high level of DNA damage could directly signal to a relevant fraction of nuclear p53. As DNA damage does not induce a change in the intracellular distribution of p53, for example into subnuclear foci, p53 does not appear to relocalize to genomic sites of DNA damage.

The conceptual problem with p53 function being impacted by p53 directly recognizing damaged DNA or DNA repair products is that the signal does not directly result in persistent alteration of p53 functions. For example, to induce G1/S arrest p53 has to travel to the genomic p53 binding sites in the p21 gene in order to transcriptionally activate p21 (Dulic et al., 1994) (Szak et al., 2001). Although p53-dependent induction of apoptosis is mechanistically disputed, transcription-independent apoptosis might require p53 to translocate to mitochondria (Mihara et al., 2003). Another problem is that if p53 binds directly to damaged DNA or repair products, relatively few molecules of p53 would receive the DNA damage signal. In contrast, indirect signaling occurring via intermediate DNA damage sensors that