The other side of p53

In vertebrates, p53 induces death or arrest in mutant cells with damaged or unstable genomes. But tumour cells can themselves induce a permissive environment yielding a highly proliferative mesenchyme that has undergone p53 loss [1, 2]. Turning on p53 may be responsible for the inhibition of cancer outgrowth with minimal toxic effects on the organism, since the stress signals activating p53 are absent in normal tissue but present in tumour [3]. In fact, this strategy had no effect on the normal tissue of mice carrying a re-activatable p53 knockout allele [4]. In mice, tumours developed in the complete absence of p53, without any selective pressure to desensitize p53 activators or downstream effectors. However, in human cancers reactivation of p53 could occur in a p53-resistant cellular environment.

Chemotherapy and radiation exposure both induce p53-dependent DNA damage, and p53 mediates cell-cycle arrest and apoptosis in response to genotoxic injury [5]. For this reason, turning off p53 function could be used to protect normal tissues from the effects of acute genotoxic stress. Delaying the restoration of p53 function until the acute radiation response has subsided, abrogates the radiation-induced pathology, preserving much of the protection from lymphoma [6]. This protection seems to be dependent on p19(ARF), a tumour suppressor induced by oncogenic disruption of the cell cycle [6].

Finally, animal models must be measured against clinical reality [1]. Nevertheless, prevention of metastatic outgrowth by strategies based on reactivation of apoptosis deserves further investigations.

G. Ferretti*, A. Felici & F. Cognetti
Division of Medical Oncology A, Regina Elena Cancer Institute, Rome, Italy
(*E-mail: gia.fer@flashnet.it)
references


doi:10.1093/annonc/mdm398