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P53: an old dog begins to learn new tricks

Since its discovery in 1979, p53 has enjoyed a remarkable life. Although innumerable molecules associated with human cancer have been identified, p53 maintains a prominent role in all fields of cancer research. Several lines of evidence implicate the involvement of p53 in the initiation, promotion and progression of human cancer. Somatic p53 alterations occur in over 50% of human cancers, whereas germline p53 mutations yield a highly penetrant (>90% lifetime probability of a carrier of a germline p53 mutation developing cancer) cancer phenotype in >75% of families with Li-Fraumeni syndrome [1]. Mutant p53 is infrequently observed in the predominantly embryonic and mesenchymal tumors of childhood, whereas it is almost ubiquitous in the epithelial cancers of adults.

The presence of mutant p53 imparts aggressive, aberrant growth properties to cancer cells, which are reflected in poorer predicted outcomes when compared with those tumors that harbour wild-type p53. p53 is also involved in the regulation of anti-angiogenic factors such as thrombospondin, which may be relevant to the invasive and metastatic properties of certain cancer cells. Recent evidence confirms the ability of p53 to traffic between the cytoplasm and the nucleus of a cell, to interact with a variety of endogenous (e.g. MDM2 and WT1) or exogenous (e.g. human papillomavirus E6 and polyomavirus large T antigen) proteins, and to adopt flexible conformations under certain biochemical conditions (e.g. thermodynamic or pH changes) that can modify its functional behaviour. These observations allow us to explore novel ways to adapt the cellular microenvironment in order to enhance the tumor suppressor properties of p53 and, in turn, modify the behaviour of the cell.

In a recent issue of *Drug Discovery Today*, Lane and Huff reinforced the idea that activation of the tumor suppressor properties of p53 are the result of numerous microenvironmental stressors that result in the recruitment of downstream mediators of cellular function, including apoptosis, growth arrest, kinase signaling, redox status and protein folding [2]. Until recently, attempts to harness the multi-faceted role of p53 in cell cycle control have concentrated primarily on gene replacement approaches. After a decade of intensive evaluation, some utility in selected tumor systems has been demonstrated in limited clinical trials. However, these approaches have been fraught with numerous difficulties, namely the mode of gene delivery, the development of effective delivery vectors and the inhibitory effects of host immune surveillance [3]. Therefore, the development of novel therapeutic approaches is required.

The quaternary structure of p53 was elucidated almost ten years ago. Recognition of its conformational flexibility and intrinsic thermodynamic instability came from the further study of mutant forms of the protein [4]. Recent advances in the design of synthetic inhibitors of a spectrum of signaling molecules, such as cyclin-dependent kinase inhibitors (e.g. p21WAF1), aberrant tyrosine kinases (e.g. bcr-abl) and signaling growth factors [e.g. vascular epidermal growth factor (VEGF) and platelet derived growth factor (PDGF)], provide a foundation for the design of drugs that might similarly affect post-translational modifications on mutant conformations of p53, thus restoring its tumor suppressor activity [5]. Lane and Huff present a comprehensive and compelling argument to support the notion that this approach will lead to the rational creation of a new class of cancer therapies. The specificity of biochemically targeted approaches might significantly diminish the toxicities commonly encountered with conventional, non-cell type-specific cytotoxic agents. Furthermore, in contrast to gene replacement approaches, host defense systems, tissue specificity, and anatomic access would not be limiting factors for drug delivery. For both patients and oncologists, such agents would carry great promise. A quarter of a century of discovery has established the foundation for us to consider p53 not only in its causative roles in human cancer, but also as a target for potentially novel and rational curative therapies. Agents such as PRIMA, Geldanamycin and others that manipulate p53 conformation to induce biologically relevant effects could soon

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become standards in the anticancer armamentarium.

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Proteasome inhibitors in the treatment of cancer

Few biochemical fields have spurred such intense interest as that of proteolytic enzymes. Initial interest in protein degradation has advanced to create a pool of knowledge that can be, and has been, exploited for therapeutic purposes: the use of recombinant tissue-plasminogen activator has revolutionized the treatment of myocardial infarcts [1]; retroviral protease inhibitors enable control over HIV infection in many patients [2]; and inhibition of angiotensin-converting enzyme is included in effective anti-hypertension treatments [3]. Numerous drugs are now being developed to interfere with proteases crucial in the coagulation, inflammation and tumor metastasis. This development was inevitable because proteasome functioning appears to be disturbed in several pathologies. Moreover, some successful drugs, such as HIV protease inhibitors, certain chemotherapeutics and statins are already effective proteasome inhibitors.

The proteasome-mediated degradation of proteins serves not only as a waste bin for aged or unwanted proteins but also as a powerful regulatory system that controls the precise timing of activation or inhibition of cellular metabolic pathways [4]. This variety of functions results from, among other factors, the fact that proteasomes can be assembled into various complexes composed of a plethora of different subunits. They can therefore target and regulate, with exquisite specificity, cellular processes as diverse as cell cycle, antigen presentation, apoptosis and transcription factor activation [4].

Owing to this versatility and the fear of unpredictable toxicity, researchers were reluctant to consider the potential use of proteasome inhibitors *in vivo*. The rapid entrance of proteasome inhibitors to clinical trials has, therefore, been an unexpected occurrence. A recent article by Julian Adams in *Drug Discovery Today* [5] provides a good summary of what has recently happened in this field.

Each class of proteasome inhibitor affects the degradation of different protein substrates. Surprisingly, some proteasome inhibitors appear to induce apoptosis in tumor cells and to protect quiescent or terminally differentiated cells. We might soon be able to precisely identify such proteasome inhibitors that will specifically affect the degradation of proteins involved in tumorigenicity and tumor progression without affecting vital cellular processes that might result in concomitant toxicity. Early observations in murine tumor models and the results of initial clinical studies are indeed encouraging and indicate feasibility, safety and efficacy of proteasome inhibitors [6–9].

Although we do not understand all of the molecular mechanisms of such anti-tumor specificity, we eagerly await the results of ongoing clinical trials, to indicate the value of proteasome inhibitors. On the one hand, they could prove to be another disappointment in the search for a cure for cancer, in which case they could still be a valuable source of more effective combinations of anti-tumor treatments (they might also reduce drug resistance, sensitize tumour cells to radiotherapy or exert anticachetic effects). On the other hand, however, proteasome inhibitors might just prove to be true magic bullets.

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