

p53-based Anti-cancer Therapies: an Empty Promise?

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Abstract

Since its discovery in 1979, p53 has become the focus of intensive cancer-based research in laboratories around the world. The p53 protein mediates critical cellular functions including the response to genotoxic stress, differentiation, senescence, and apoptosis, and has been shown to be mutated in a large proportion of human cancers. These observations led many to speculate that targeting the p53 pathway would result in the development of successful anti-cancer treatments. In spite of this, 30 years later, p53 has yet to fulfill this promise. However, new insights into small molecule combination therapies, microRNA regulation, structuring of clinical trials, and potential involvement in stem cell regulation may help p53 reach its potential.

The Promise

The p53 protein was identified in 1979 by co-immunoprecipitation of p53 with T-antigen in SV40-transformed cells (Chang et al., 1979; Kress et al., 1979; Lane and Crawford, 1979; Linzer and Levine, 1979; Melero et al., 1979). It was further noted that the p53 protein was overexpressed not only in SV40-transformed cells, but also in carcinoma cell lines (Linzer and Levine, 1979; for a detailed historical review of p53, see Hainaut and Wiman, 2009).

Early work implicated p53 as an oncogene (Eliyahu et al., 1984; Parada et al., 1984); however, it was subsequently determined that a mutant version of p53 was utilized in these studies (Hinds et al., 1989). Successive studies using wildtype p53 supported the conclusion that p53 acts instead as a tumour suppressor (Baker et al., 1989; Finlay et al., 1989; Hinds et al., 1989). Following these discoveries, p53 was dubbed “guardian of the genome” (Lane, 1992) and *Science*’s “Molecule of the Year 1993”.

Since then, p53 has been shown to play a role in response to genotoxic stress, differentiation, senescence, and apoptosis, and is one of the most commonly altered proteins in human cancer (Chari et al., 2009). Consequently, many laboratories have dedicated considerable time and resources with the intention of developing therapies aimed at restoring wildtype p53 activity in cells with mutated p53 or by inhibiting a key negative regulator of p53, such as murine double minute 2 (MDM2; Vazquez et al., 2008). Though a wealth of information has been accumulated in this area, p53-based research has not yet had a wide impact on cancer management and therapy (Hainaut and Wiman,

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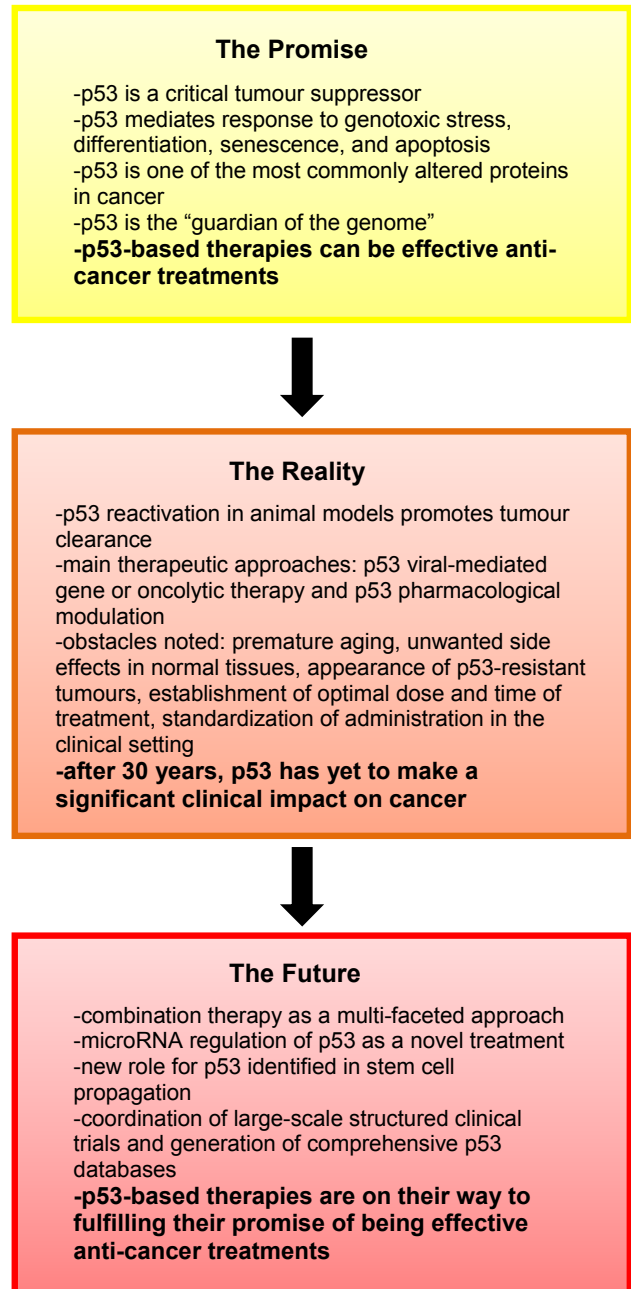


Fig. 1. The promise, the reality, and the future of p53-based anti-cancer therapies.

2009) and the question remains as to whether the promise of p53-based anti-cancer treatments will turn out to be an empty one (Figure 1).

The Reality

Numerous approaches have been applied to generate p53-based anti-cancer therapies. Such approaches include: retrovirus- or adenovirus-mediated gene therapy to restore

p53 function, killing of p53-deficient cells with modified adenoviruses, and pharmacological modulation of p53 protein functions (Bouchet et al., 2006). Studies have also taken place to identify drugs and mechanisms that activate p63 and p73, since these proteins are not mutated in cancers and as such are potential candidates for replacing p53 in p53-deficient cells (Alsafadi et al., 2009).

Recent genetic studies in mouse models have shown that reactivation of the p53 pathway in tumours with reduced or no p53 activity promotes tumour clearance, renewing interest in and providing further strong evidence for designing anti-cancer drugs that restore p53 function (Ventura et al., 2007; Xue et al., 2007; Vazquez et al., 2008; Shangary and Wang, 2009). Among the different strategies for restoring p53 function, targeting the MDM2-p53 interaction by small molecules has proven to be popular. MDM2 has been shown to inhibit p53 by regulating its subcellular location, its stability, and its transactivation function (Vazquez et al., 2008; Shangary and Wang, 2009). Historically, disruption of protein-protein interactions has been a daunting task due to the typically large binding region of the protein partners. However, the MDM2-p53 interaction has been mapped to a small, well-defined interface, opening the door to the possibility of interference by small molecule inhibitors. Different approaches have been used to identify and design small-molecule inhibitors of the MDM2-p53 interaction. These include: 3D database screening of large chemical libraries, experimental screening of chemical libraries, and structure-based *de novo* design (Shangary and Wang, 2009). These approaches have generated a number of potential therapeutic agents (Nutlins, benzodiazepines, reactivation of p53 and induction of tumour cell apoptosis [RITA], spiro-oxindoles, and quinolinols) for interference with the MDM2-p53 interaction, however, the efficacies of such treatments in humans remain to be determined (Vazquez et al., 2008).

Interestingly, accumulating observations of p53 activity *in vivo* in experimental animals indicate that the same p53 tumour suppressive functions can be harmful under conditions of systemic genotoxic stress such as total body irradiation or injection of genotoxic anti-cancer drugs (Gudkov and Komarova, 2007). By comparing tumour models differing in stromal p53 status, Burdelya et al. (2006) showed that tumours with p53-deficient stroma were significantly more sensitive to experimental chemo- and radiotherapy than tumours with wildtype p53 stroma. Thus, temporary and reversible suppression of p53 may be beneficial for prevention and treatment of acute conditions associated with severe genotoxic stress (Gudkov and Komarova, 2007).

Despite the intensive p53-based therapeutic research and numerous discoveries presented above, reality dictates that significant challenges and unresolved issues need to be addressed before p53-targeted therapies find clinical application. Examples of such obstacles include: premature aging, unwanted side effects in normal tissues, appearance of p53-resistant tumours, establishment of optimal dose and time of treatment, and standardization of administration in the clinical setting (Bouchet et al., 2006; Fuster et al., 2007).

The Future

Recent discoveries complement the last 30 years of p53-based research. Insights into small molecule combination treatments, microRNA regulation of p53, potential involvement of p53 in stem cell regulation, and coordinated restructuring of clinical trials with compatible comprehensive databases will likely accelerate the development of p53-based anti-cancer therapies.

Due to the recognized heterogeneous nature of cancer, combination therapies are increasingly being proposed as more effective strategies. In the case of p53-based treatment approaches, promising results have been seen by combining small molecule inhibitors with various other anti-cancer agents. For example, Graat et al. (2007) demonstrated enhanced tumour cell kill with a combination of the MDM2 antagonist Nutlin and adenovirus-mediated p53 gene therapy. The authors also tested Nutlin in combination with oncolytic adenovirus-infected cancer cells, revealing accelerated viral progeny burst and a 10-1000-fold augmented eradication of p53 wildtype cancer cells. Cheok et al. (2007) also highlighted the potential success of Nutlins as therapeutic team members, but in a different manner. In this case, statistical measurement of the combination of cyclin-dependent inhibitors and Nutlin-3a demonstrated an additive effect on the reduction of cell viability and apoptotic induction in melanoma, colon carcinoma, breast adenocarcinoma, and hepatocarcinoma cells. Recently, Canner et al. (2009) demonstrated that treatment of rhabdomyosarcoma cells with the small molecule inhibitor MI-63 in combination with the known chemotherapeutic agent doxorubicin resulted in a synergistic effect. As doxorubicin may act in a p53-independent manner, the authors hypothesized that a combination treatment with MI-63 would potentiate each drug's anti-proliferative effects. In accordance with this, 20 nM of doxorubicin in combination with 2000 nM MI-63 (day 1), showed a 49% increase in the fraction of cells affected by treatment when compared with the expected additive effect. Clinical trials will be necessary to evaluate such combinatorial effects for future therapeutic usage.

MicroRNAs (miRNAs) are small (18-25 nt), noncoding RNAs that function by controlling protein expression of other genes (Metias et al., 2009). miRNAs have recently stolen some thunder from small interfering RNAs (siRNAs; Campbell and Choy, 2005) as potential diagnostic and therapeutic tools. Specific miRNAs have been identified as inappropriately expressed in a variety of different tumours, leading to the speculation of linkage to cancer (Chari et al., 2009). Several members of the miRNA-34 family have been shown to be downstream mediators of p53-induced apoptosis, cell cycle arrest, and senescence (Bommer et al., 2007; Chang et al., 2007; Corney et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Chari et al., 2009). Recently, the presence of a positive feedback loop was demonstrated in which p53 upregulated miRNA-34a, which then repressed the NAD-dependent deacetylase silent information regulator 1 (SIRT1), resulting in increased levels of p53 and amplification of the apoptotic signal (Yamakuchi et al., 2008). Such observations provide the impetus to move forward with manipulation of microRNAs for the development of p53-based anti-cancer treatments.

Published in late 2009, results from five independent laboratories identified p53 as a critical checkpoint during

the multifactor reprogramming process whereby induced pluripotent stem cells are derived from differentiated adult cells (Hong et al., 2009; Kawamura et al., 2009; Li et al., 2009; Marion et al., 2009; Utikal et al., 2009). Absence of functional p53 enhanced the yield of induced pluripotent stem cells in each case, implicating p53 as a major gatekeeper of self-renewal (Aparicio and Eaves, 2009). This both complicates and enhances the role p53 may play in anti-cancer therapies. For example, if cancer is shown to arise directly through reprogramming-like processes, then further studies into reprogramming and the subsequent role of p53 may eventually point towards new, effective treatment for cancers (Krizhanovsky and Lowe, 2009).

Hainaut and Wiman (2009) stress the need for large, structured clinical trials in which patients with defined p53 status are specifically recruited, randomly assigned to predetermined treatment regimens, and followed up for long-term therapeutic and clinical endpoints. They advocate that detailed understanding of the clinical significance of p53 status will come from pooled analyses and meta-analyses assessing the strength of evidence across large data sets and different study contexts. This restructuring and amalgamation of clinical trials will expedite the process for determining the prognostic and predictive value of p53 mutations, as well as contribute to the eventual pharmacological control of p53 in cancer therapy, improving both survival and quality of life for cancer patients.

In concert with the restructuring of clinical trials, the strengthening and integration of current comprehensive online knowledgebases and datasets (Lim et al., 2007; International Agency for Research on Cancer TP53 database, <http://www-p53.iarc.fr/>) will permit rapid access to all relevant p53-related information (Hainaut and Wiman, 2009). The collection and dissemination of such a broad spectrum of research will provide insight into the interconnectedness of biological processes and allow rapid correlation with clinical data, accelerating the impact on disease diagnosis and treatment.

Summary

Time will tell whether p53 will fulfill its promise of playing a leading role in anti-cancer therapies. Regardless, the amassed knowledge of p53 biology provides a valuable resource for uncovering new ways to approach and manage cancer.

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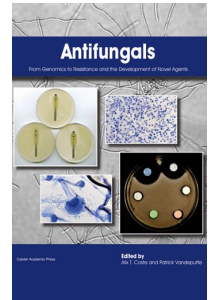
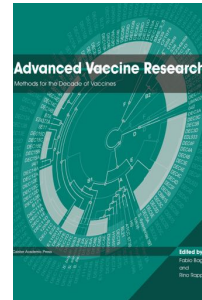
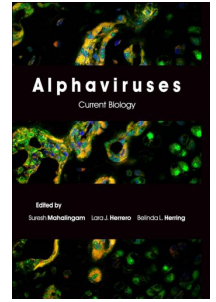
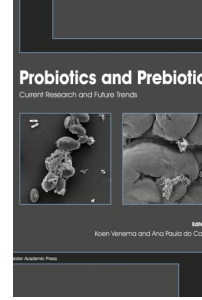
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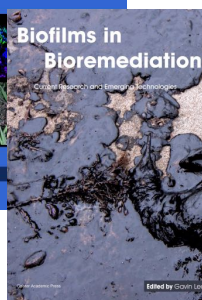
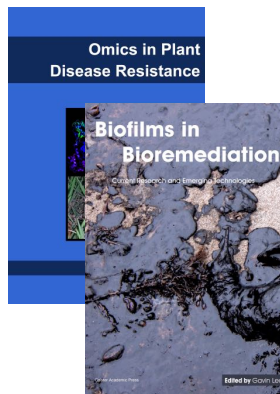
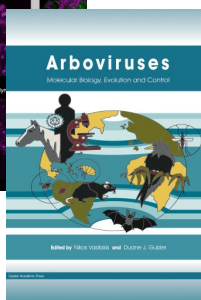
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