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Editorial

Cancer Therapeutics Beyond 2000 – More Rationality, Less Empiricism

H L Kong

INTRODUCTION

Despite major advances in cancer surgery, radiotherapy and chemotherapy over the past 4 decades, approximately half of all cancer patients still die of their malignancies. There are reasons to believe that current modalities of cancer therapy will not achieve a quantum improvement in the treatment outcome. Therefore, finding innovative ways of tackling cancers is absolutely imperative. Over the past two decades, we have witnessed an explosion in our fundamental understanding of cancer biology. Cancers, and indeed other diseases as well, are now being defined at sub-microscopic levels, ie., in molecular and the genetic dimensions. Armed with this powerful knowledge, we are now poised to confront the treatment of cancer in the next millennium with a hitherto unseen rationality and confidence. In parallel, the increasing number of clinicians-scientists in Singapore in recent years will enable us to rapidly translate laboratory advances to clinically beneficial tools. Two novel and exciting cancer therapies will be described to illustrate how we can now tailor the treatment of cancers to their underlying molecular and genetic aberrations.

Cancer gene therapy

"Human gene therapy – an immature genie, but certainly out of the bottle."

– Theodore Friedman, 1996

Gene therapy, broadly defined, is the introduction of nucleic acids (DNAs and RNAs) into somatic cells for therapeutic purposes. It is the use of genes as drugs. Gene therapy introduces normal genes into cells which are deficient in them (gene replacement), or introduces specific genes whose expression leads to new biological effects that are therapeutic to the diseased hosts (creation of new cellular functions)[1]. Gene transfer vehicles, or gene vectors, are needed to ensure that the genes are efficiently translocated to the nucleus, where the transcriptional machinery resides. Gene vectors in use today include both viruses and non-viral agents. Viruses are gene vectors par excellence. Genetic modifications of viruses render them non-pathogenic, but yet retain their innate ability to efficiently transfer their genetic payloads, an ability which the viruses have evolved to a state of near-perfection over millions of years[1,2]. In contrast to conventional drug therapy, gene therapy has the potential advantages of inducing prolonged therapeutic effects (like a slow-release drug preparation), and of localising the treatment effects to specific target tissues, thereby avoiding unintended injury to non-diseased organs[1].

More than 60% of clinical gene therapy trials pertain to cancers. The strategies employed include: replacement of missing tumour suppressor gene function (eg. p53 gene); use of antisense nucleic acid sequences to inactivate oncogenes; use of "suicide genes" which convert relatively innocuous prodrugs (eg. 5-fluorocytosine, an antifungal) to cytotoxic agents (eg. 5-fluorouracil) within the transduced cells; generation of tumour-specific immunity; and introduction of genes which suppress tumour neovascularisation[2-4].

Although imaginative investigators already speculated the concept of gene therapy in the 60s and 70s, it was not until the late 80s before these speculations

could be put to scientific test. The catalyst was the birth of the recombinant DNA technology, allowing us to manipulate genes at will. The first human gene therapy trial was carried out in the US in 1990. Since then, more than 7000 papers on preclinical and clinical gene therapy have been published, and more than 230 human gene therapy trials have been approved in the United States. Complete disappearances of animal tumours and prolongation of survival have been well documented, thereby establishing the proof of principle in gene therapy beyond doubt. However, over the same 8 years, we have also witnessed a large number of early clinical trials which did not establish clear treatment efficacy. One reason for this apparent failure is that these trials are largely phase I in design, seeking to demonstrate safety profile and biological effects rather than treatment efficacy. Other deficiencies in the early gene therapy trials were the use of relatively unsophisticated vectors, and the inclusion of patients who invariably had advanced and bulky cancers[2].

In the past two to three years, however, newer-generation vectors have been constructed, with enhanced capabilities such as improved tumour-targeting, more prolonged or even regulatable gene expression[2]. For instance, we now have vectors which express their genes specifically in carcinoembryonic antigen (CEA)- or alphafetoprotein (AFP)-producing cells.

We are also beginning to realise that gene therapy is most likely to work best if the tumours are not widely disseminated and are not bulky. Indeed, gene therapy as an adjuvant treatment after surgical debulking of localised tumours will undoubtedly be intensely examined in the coming years. These recent advances augur well for the future of gene therapy. Judging from the phenomenal progress which the field of gene therapy has made in just a few years, one can conclude that although gene therapy is yet to come of age, there can be no doubt that, in time, it will bear fruit[2,3].

Antiangiogenesis

"Once tumour take has occurred, every increase in tumour cell population must be preceded by an increase in new capillaries"

– Judah Folkman, 1971

Judah Folkman first hypothesised in the 70s that tumour growth beyond 1 – 2 mm^3 would require the formation of new blood vessels within the tumours. However, it was not until the late 80s that this simple hypothesis was validated[5]. The proteins which drive the cascade of angiogenesis, eg. vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), have been well characterised in the past decade. Given the critical dependence of tumour growth and metastasis on angiogenesis, it is conceivable that interruption of this pivotal biological process in cancer may be therapeutic[1,5].

Over the past 15 years, a number of endogenous or synthetic compounds have been discovered which can inhibit angiogenesis, both in vitro and in vivo. This has triggered off a zealous effort world-wide to induce antiangiogenesis with a therapeutic intent. In animal tumour models, drugs such as angiostatin and endostatin have been shown to spectacularly inhibit tumour growth. More than two dozens phase I/II antiangiogenesis clinical trials are now underway in the US, including the use of suramin, marimastat, TNP-470 (AGM-1470), and thalidomide[1]. While it is still too early to draw any firm conclusion from these trials, a few important principles of tumour antiangiogenesis have emerged[1,5]. Firstly, antiangiogenesis is likely to be applicable to a large number of tumour types, both solid and liquid tumours, given the universal requirement of malignant cells for neovascularisation. Secondly, since antiangiogenic drugs are believed to be cytostatic rather than cytotoxic, they are generally less toxic to the hosts, but they have to be applied over a prolonged period of time so as not to lose their therapeutic effect. Thirdly, experiments in animal systems have shown that tumour-associated endothelial cells, which are non-malignant per se, are very unlikely to develop resistance to the antiangiogenic drugs. Finally, it is likely that antiangiogenesis treatment will operate best in low tumour burden situations.

A very recent movement to employ gene transfer techniques to achieve tumour antiangiogenesis has documented very dramatic tumour suppression and prolongation of survival in treated animals[4]. Gene-mediated antiangiogenesis has the potential advantage of a more sustained and targeted therapeutic effect than conventional drug delivery. Being able to target antiangiogenesis to only cancer-bearing tissues is clearly advantageous, as it avoids inhibition of physiological angiogenesis, such as the female ovulation cycle, wound healing and tissue response to hypoxia[1].

Conclusions

The two novel cancer therapies presented above illustrate how basic scientific information can be effectively used to design rational cancer treatment. While neither gene therapy nor antiangiogenesis is likely to replace conventional cancer treatment in the next decade, we are likely to see them providing alternatives to, or complementing, existing treatment modalities[1,2]. As we are assessing the clinical potential of successful manoeuvres in the laboratory, we must realise that men are not merely large mice. Besides the obvious differences in size and outer appearances, the two species are very different in genetic and other biological characteristics. As such, one cannot simply extrapolate results from animal experiments to human subjects. Properly conducted clinical trials are still necessary to validate the clinical utility of promising novel therapies such as cancer gene therapy and antiangiogenesis. However, we must also not forget that the seeds to these human trials are first sowed in the test tubes and the animal laboratories.

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