EDITORIAL

Molecular Genetics in Gynaecologic Cancer and its Clinical Implications

It is a most relevant statement made today that we are entering into a genetic age. Two genetic scenarios; (i) the accumulation of mutations that are exclusively somatic in origin and (ii) the inheritance of a mutation(s) through the germ line followed by the acquisition of additional somatic mutations are colloquially referred to as sporadic and heriditary cancers, respectively. There are two classes of genes subject to mutation in human cancers, Oncogenes and Tumour suppressor genes. Oncogenes are most frequently altered through point mutation or gene amplification which serve to increase the activity or amount, respectively of the encoded protein. Oncogenic point mutations typically involve missense alterations in which the substitution of one nucleotide for another changes the amino acid at a codon critical in determining the activity of the protein. Gene amplification involves the formation of multiple copies of an otherwise single – copy gene, effectively increasing the amount of an oncogenic protein in the cancer cell. The amplified gene copies may exist within a chromosome, where they often appear as homogeneously staining regions, or as small extra chromosomal fragmants known as double minutes. Less common are chromosomal translocations, which may also activate oncogenes when they become juxtaposed with a foreign promoter element that increases the basal transcription level of the oncogene deregulating its expression.

Tumour suppressor genes sustain loss of function alterations, the most common of which are frame shift and nonsense mutations. The frame shift mutation involve the insertion or deletion of a small number of nucleotides such that the reading frame for the encoded protein is altered downstream of the mutation. While the new reading frame always encodes an unrelated protein sequence, most often a premature stop codon is encountered shortly after the mutation, as there is typically only one open reading frame for a gene. When premature stop codons result from a mutation, they are known as nonsense mutations. Less common are large genomic deletions resulting in the loss of a large portion or all of a gene. While translocations may theoretically disrupt tumour suppressor genes, there is little precedent for this mechanism in human cancer genetics.

Cancer genetics research would have been science fiction a decade ago. Today detection of mutations predisposing to cancer is possible in about twenty genes. What does the future hold for the explosive advances in molecular genetics ? Cancer susceptibility gene contributing to most major familial cancer syndromes remains to be discovered. Identification of these genes will likely be achieved through continued recruitment of high–risk families to establish research programmes. Once identified, clarification of the function of these cancer genes will help us understand better their

roleplay in tumourigenesis. This knowledge will be important in developing effective interventional strategies such as cancer surveillance, prophylactic surgery, chemoprevention and possibly gene therapy that will hopefully reduce morbidity and mortality in these syndromes.

Genetic based therapy is a novel therapeutic approach to treat cancer which has been made possible only by recent remarkable progress in our understanding of the molecular biology of cancer. Gene therapy can be described as the transfer to, and expression of, genetic material in human cells for a therapeutic purpose. The increase in the number of potential methods of gene delivery reflect rapid technological advances in this field. Molecular intervention may be "direct" and manipulate tumour cells by altering the genome by the ablation, addition or substitution of specific DNA sequences. The choice of these depends on the underlying genetic defect. Some strategies can be achieved by ex vivo gene transfer into isolated human cells which can then be reimplanted into the host, while others require delivery and expression of genes to target cells in vivo–a major challenge with current vector technology.

The challenges to make gene therapy an effective and broadly useful treatment modality are formidable not only with the limitations in efficiency and targetting of gene transfer vectors but also without incomplete understanding of control of gene transcription and th long term consequences of constitutive expression of transferred gene. There are now over two hundred activ protocols for cancer. In the short term, furthe improvements will come from refining currently use vectors and the design of a new generation of vecto incorporating the most useful aspects of viral an synthetic systems, which can then be applied to a specific cancer target. In the long term, we envisage th construction of artificial chromosomes which could car whole clusters of genes with their natural contr elements into cells. There is no shortage of ideas and t applications in this advancing field and shortly w anticipate the proposal of clinical protocols for ge therapy for a spectrum of diseases. We should optimistic about patients with otherwise unresponsi cancers, as there is every indication that this treatme modality will make an impact in the near future.

References

1. Boyd J, Narrett JC. Genetic and Cellular basis of multi s Carcino genesis. *Pharmacol Therap* 1990; 46 : 469.
2. Olah E, *et al.* BRCAI mutation in Hungarian breast andOva Cancer families. *Magyer onkologia* 1997; 41 : 69.
3. Sikora K. Genes, dreams and cancer. *BMJ* 1994; 308 : 12

Prof. KASTURI L
Formerly Prnc
Govt. Medical College, Jammu (J&
Presently Director Institut
Obstetrics, Gynaecolgy and Child He
Jammu (J&