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CANCER AND THE RESPIROME

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1. INTRODUCTION

It is now over 80 years since Warburg first described the tumour respiratory phenotype. During that time great advances have taken place in terms of our understanding of the mechanisms and control of respiration and our understanding of the genetic processes that predispose some individuals to a higher risk of cancer. Warburg's original description of the cancer phenotype as being hypoxic or anoxic still applies to many advanced cancers but we now know that during tumourigenesis there is great variability in the oxygen metabolic status of individual tumours.

A fundamental contribution to our perception of the cancer process was the description of genes that were altered in individuals with familial cancers. That discovery emerged from basic science research into cancers that were virally transmissible between animals. From those studies emerged the concept of oncogenes and their translation products the oncoproteins. Oncogenes, being dominantly expressed, exert their phenotypic influence by gain of function. By contrast, the tumour suppressor genes, whose description followed soon after the discovery of oncogenes, are recessive genes and are expressed through loss of function. Although the majority of oncogenes and tumour suppressor genes were discovered before the end of the last millennium, it is only in the light of the publication of the results of the human genome projects that we can begin to analyse whether there might be any relationship between the genetic injury in a particular cancer and its respiratory phenotype. Potentially, this has important implications for the way in which treatment might be approached in particular patients or groups of patients.

The two human genome projects, one driven by government altruism and the other by commercial interest were commenced in the late 1980s and their results published in concurrent articles in December 2000. Even a cursory analysis of those results leaves the impression that there is much yet to be learnt about our inheritance. Nevertheless, the

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resources provided by these two endeavours provide us with unprecedented opportunities to examine links between genotype and phenotype in cancer mutation sites and respiratory components. The competition to win the human genome race has also spawned a valuable coterie of new techniques and technology that make this task achievable on even modest research budgets.

One of the important outcomes of the discoveries to emerge from the human genome projects has been a revision of the central dogma of molecular biology, which was already shaking under the impact of the discoveries of reverse transcriptase viruses and of prions. The central dogma of molecular biology as initially enunciated, described the process by which the genetic information of any organism is first transcribed from DNA into messenger RNA (mRNA) and then translated into protein sequence.

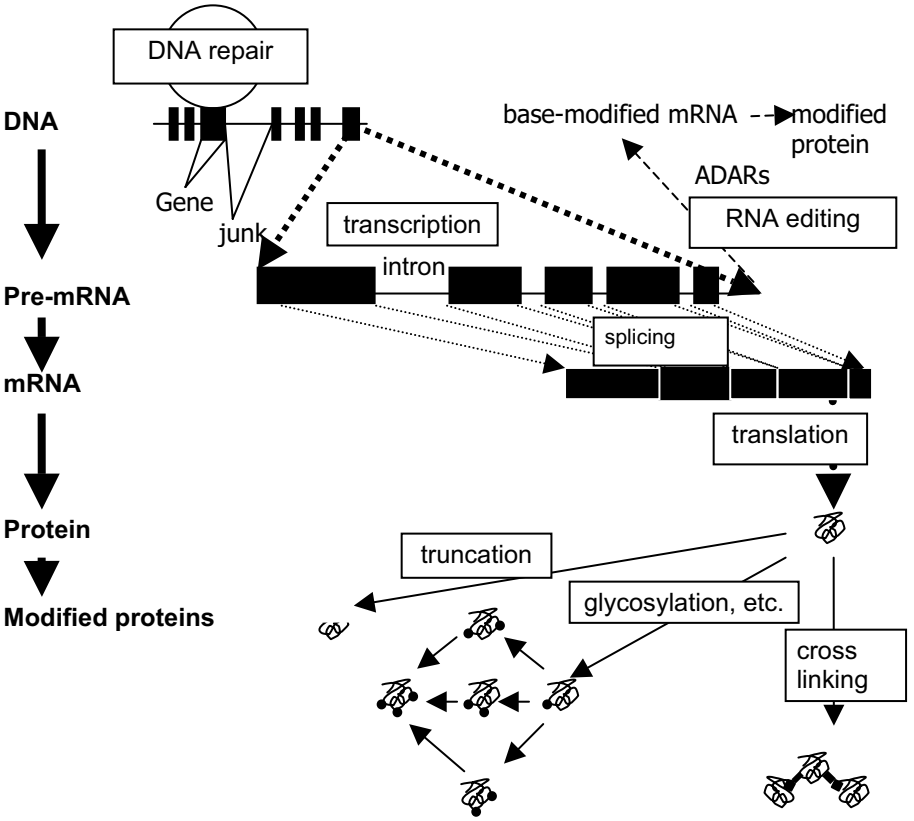

Figure 1. Overview of the central dogma of molecular biology as it applies to humans; ADAR, adenosine deaminase acting on RNA.

2. REVISED CENTRAL DOGMA OF MOLECULAR BIOLOGY

Advances in our understanding of how genes are decoded and expressed have forced a revision of each of the steps in this process. The process, as it operates in humans, is