REVIEW

How do mutated oncogenes and tumor suppressor genes cause cancer?

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In recent decades we have been given insight into the process that transforms a normal cell into a malignant cancer cell. It has been recognised that malignant transformation occurs through successive mutations in specific cellular genes, leading to the activation of oncogenes and inactivation of tumor suppressor genes. The further study of these genes has generated much of its excitement from the convergence of experiments addressing the genetic basis of cancer, together with cellular pathways that normally control important cellular regulatory programmes. In the present review the context in which oncogenes and tumor suppressor genes normally function as key regulators of physiological processes such as proliferation, cell death/apoptosis, differentiation and senescence will be described, as well as how these cellular programmes become deregulated in cancer due to mutations.

Keywords: oncogenes; tumor suppressor genes; proliferation; apoptosis; differentiation; senescence

Introduction

It is today clear that cancer is caused by specific mutations in specific key regulatory genes. Since the discovery of the first such genes some 30 years ago, we have seen remarkable progress in the definition of genetic lesions in malignancy, and furthermore our general understanding of cell biology has made us able to comprehend how these cancer genes normally function in the control of the non-malignant cell, and how this relates to the ability of these genes to cause malignant transformation when mutated.

In normal tissues of multicellular organisms the function of the single cell is tightly controlled due to inner and surrounding constraints, to maintain tissue homeostasis and function. During malignant transformation the cancer cell will gradually become more autonomous, and develop into an 'asocial citizen' of its tissue, growing in an uncontrolled manner at the expense of the function of the normal tissue. More specifically, the cancer cell has obtained relaxed control of several normal cell regulatory mechanisms. The most obvious such function is proliferative control. In many types of malignancies (but not all), the tumor cells divide at a higher rate, often irrespective of the extracellular growth signals that usually control cell growth. Although obvious today, it was not until recently that it was realised that tissue growth is not only regulated by the rate of cell division, but that the rate of cell death or apoptosis is another key factor in tissue homeostasis.

With this came the understanding that malignancy may also develop through reduced cell death rate. Furthermore, a common feature of cancer cells is their inability to differentiate terminally, which in normal tissues would lead to cessation of proliferation. Cell cultures derived from human tumors often divide indefinitely; furthermore, the number of population doublings a cell has to go through in order to become a clinically detectable tumor is very large. This is in sharp contrast to non-transformed cells which, with few exceptions, have a limited lifespan and will, after a defined number of population doublings, enter a non-

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repetitive but metabolically active state termed senescence.\(^3\) This has led to the hypothesis that cellular senescence is a tumor suppressor mechanism which is abrogated in malignancy.\(^3\)

As previously mentioned a number of genes that are specifically mutated in malignant cell have been defined to date. They can generally be divided into two groups: oncogenes and tumor suppressor genes. Oncogenes take part in malignant transformation due to activating mutations such as amplification, small mutations or translocations. Due to their activating nature, mutations in these genes are usually dominant and only one allele of the gene needs to be affected. The function of tumor suppressor genes on the other hand seems to be to protect the normal cell from developing into a cancer cell, and a loss of their function leads to malignant transformation. As the majority of human genes are present in two copies in the genome, both alleles usually have to be inactivated for their tumor-suppressing activity to be lost. Recently a third category of cancer-related genes has been defined; namely the DNA repair genes. These are a group of genes that take part in the normal repair of DNA damage, and somatic or inherited loss of their function leads to an increased frequency of secondary mutations in oncogenes and tumor suppressor genes.\(^5\) With the definition of the molecular background of a number of different inherited cancer syndromes, it has been shown that the increased cancer risk in these families may often be due to the inheritance of a mutated tumor suppressor gene.

The present review will not give a detailed list of known cancer-related genes, but will rather describe the normal context in which these genes regulate physiological processes such as proliferation, cell death/apoptosis, differentiation and senescence, and how they become deregulated in the malignant cell due to mutations in oncogenes and tumor suppressor genes. The review will not deal to any major extent with other factors that may be of importance in the malignant process, such as the mechanism behind the acquisition of metastasising potential or the interaction of tumor cells with surrounding stroma and blood vessels.

**Proliferation**

Our understanding of the regulation of eukaryotic cell division took a quantum leap some ten years ago, when it was realised that cell cycle progression is governed by sequential formation and activation of enzyme complexes consisting of a family of related cyclin-depend-ent serine-threonine kinases (cdks) and their cyclin partners (for a review see Ref. 6). At the various cell cycle phases, waves of kinase activity corresponding to different family members of the cdks will propel cells through the periodic events of mitotic division by phosphorylation of key substrates. The activity of these kinases is positively and negatively regulated by various growth regulatory signals. Positive external mitogenic signals will come from stimulation of the cell by various growth factors through binding to their specific cell surface receptors. Growth factor stimulation will lead to activation of intracellular signalling systems such as membrane associated enzymes and transcription factors. These events will affect the cdks active in the G1 phase by increasing cyclin levels as well as changing the phosphorylative status of the cdks themselves, leading to full activation of these kinases and permitting further progress in the cell cycle (see Figure 1). One of the major substrates for the activated kinases in the G1 phase is the retinoblastoma protein (pRb). When pRb becomes phosphorylated by the kinases this will lead to release of a group of transcription factors of the E2F family that activate genes essential for S phase such as DNA polymerase alpha, and c-myc (see Figure 1). Several observations suggest that the phosphorylation of pRb by the cyclin–cdk complexes is a rate-limiting step in G1 progression. After this point cells become committed to cell division irrespective of whether growth factors are present or not.\(^7\) This event has previously been termed the ‘restriction point’.

The cdks can also be negatively regulated by the newly discovered cdk inhibitors (ckis). These latter inhibitory proteins have been found to be important effector molecules for internal and external growth inhibitory signals such as DNA damage, contact inhibition and the cell growth inhibitory cytokines TGFB and interferons.\(^8\)

As previously mentioned, uncontrolled growth is a common feature of malignant cells. Genes that control the decision to initiate a new round of DNA synthesis are attractive candidates for oncogenes and tumor suppressor genes, depending on whether they have a stimulatory or inhibitory role in the process. Indeed, several oncogenes and tumor suppressor genes have been found to participate directly in cell cycle regulation.\(^1,6\) For example the malignant cell may have mutations in genes leading to an autonomous production of growth factors, constitutive activation of growth factor receptors or membrane-bound signalling proteins, leading to more or less autonomous growth. It has also become clear that malignant cells commonly carry