Differentiation: an encouraging approach to anticancer therapy

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SUMMARY

Differentiation is a complex multistep process of cell specialization that begins with the installation of a genetic programme, named determination, specific for a cell lineage. Development of the differentiation programme includes the cell-type specific silencing of some genes and the expression of other genes, that regulate the biological functions associated with the cellular type and that distinguish the specialized cells. Terminal differentiation is the end stage of this process where the cells irreversibly lose their proliferative capacity and which represents a form of negative control of growing. Regulating molecules interact to produce the correct balance between cellular multiplication and differentiation during embryogenesis and the normal behaviour of an adult.

Cancer is a process in which changes in regulating circuits are produced, such as proliferation control, the balance between cellular survival and programmed cellular death (apoptosis), the communication with neighbouring cells and with the extracellular matrix, angiogenesis, and finally, the migration of the tumoural cell, the invasion and metastasic dissemination. This process implies the progressive development of a more malign phenotype with an increase of genetic alterations involving genes at several levels of expression during long periods of time. These genetic changes uncouple the normal balance between multiplication and cellular differentiation with an increase in the rate of proliferating cells.

Classic chemotherapeutical agents have been very important; nevertheless, as the mechanism of action of these drugs depends on the cytodestruction of the neoplastic cells, their beneficial effects are normally accompanied by a notable morbidity, cytotoxicity and multidrug resistance. The

knowledge of the mechanisms involved in differentiation and malignant transformation has allowed the search of alternative routes for antitumoural therapy that does not imply cellular death. Differentiation therapy focuses on the development and use of specific agents designed to selectively attract the terminal differentiation process, making the elimination of tumoural cells feasible together with the establishment of normal cellular homeostasis.

INTRODUCTION

The approximately thirty billion normal cells that make up a healthy body live interdependently so that some of them regulate the proliferation of the others to favour the survival of the whole organism. Each tissue sustains its structure and size by means of this collaboration, which consists in complex signalling mechanisms that allow the cells to grow and differentiate in a coordinated manner, and maintains the internal medium in balance. Accordingly, in normal conditions there exists an equilibrium between proliferation and cell differentiation. Nevertheless, when both this balance and coordination are broken the malign transformation takes place, shifting the balance in favour of proliferation to the detriment of differentiation.

Tumoural cells do not comply with the normal proliferation controls by the neighbouring cells and start to reproduce continuously. Cancer begins when a normal cell, which replicates only slightly or not at all, suffers a somatic mutation in a gene and starts to proliferate uncontrollably. Everything indicates that at least six or seven successive mutations are necessary to change a normal cell into an invading carcinoma and demonstrates the monoclonal origin of tumours, *i. e.*, a population or cellular clone is produced from a mutated cell, in which each one of its components reproduces the mutation (Weinberg, 1989). The molecular defects that must occur for the transformation of a normal cell into a tumour cell result in six essential alterations in cell physiology: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue evasion and metastasis (Hanahan and Weinberg, 2000). All these changes are the consequence of the genome instability because of the malfunction of the repair systems.

Differentiation is a complex multistep process that affects many biological processes that regulate the expression of lineage-specific genes, and it regulates cell proliferation (Wang and Scott, 1994). In cancer, neoplastic cells exhibit defects in their ability to differentiate, and the development of defects in the process of differentiation appears to be an intimate part of the transformation process. Moreover, neoplastic transformation does not necessarily destroy the potential for the expression of differentiated characteristics, including the cessation of proliferation under appropriate environmental conditions (Marks et al., 2000). Some malignant cells (e.g., from leukemias, neuroblastomas, carcinomas, or teratocarcinomas) can differentiate along apparently normal pathways when placed in a normal embryonic environment (Gootwine et al., 1982).