patients we are dealing with. In fact, given the favorable outcome of APL with front-line RA plus chemotherapy, only few patients may be the subject of investigation for treatment of relapse.[5-7] Finally, the effectiveness of As_2O_3 for consolidation of RA+chemotherapy induced remission as well as its potential synergism with retinoids front-line are being assessed in ongoing studies.

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Cell division cycle manipulation and cancer treatment: a solid promise or just a dream?

The exact number, function and phenotype of cells present in a specific tissue are under a strict control which results in a wonderful balance between a resting status, proliferation, differentiation (both terminal or reversible), and apoptosis.

Cancer might be thought of a disease characterized by a deregulation of this balance with a partial loss of differentiation features and apoptotic response along with a relative increase of proliferative capability. Thus, it is not surprising that the molecular components of the cell division cycle machinery are frequently altered in human neoplasias. The cell-cycle of all post-embryonic eukaryotic cells (including malignant cells) is divided into four phases, namely: G1 phase (the period prior to DNA synthesis), S phase (period of DNA synthesis), G2 phase (period between DNA synthesis and mitosis) and M phase (mitosis). Collectively, G1, S and G2 are called the interphase, the cell cycle period distinct from division of the nucleus (mitosis) and cytoplasm (cytokinesis).[1-3]

The duration of the S, G2 and M phases are remarkably similar in many different cells, while the greatest variation is seen in the duration of G1. At some point late in G1, called the restriction or R point, a cell becomes committed to go through the remainder of the cell cycle. Thus, variations in cell cycle time are mostly due to variations in the length of G1 up to the R point.[1-3]

A large body of evidence indicates that transformed cells show alterations which involve the mechanisms regulating the transversing of the R point and result in a premature S phase entry. Such a phenomenon might cause ineffective DNA repair, the accumulation of genetic damage and, finally, the progression towards a malignant genotype. As well known, most of these aberrations cause the loss of activity of *RB*, *p53* and *CDKN2A* (*p16^{INKa}*) genes.[4-6]

Additional type of alterations, particularly overexpression, have been evidenced in several other genes encoding proteins which regulate some step of cell division cycle. Their frequency is, however, lower than that of the three genes mentioned above. In conclusion, it has been generally thought that all human cancers show at least one genetic aberration which allows the loss of cell cycle control.

A logical consequence of these premises is that approaches which might restore physiologic control of the cell cycle could be useful in the treatment of cancer. These are the bases of the study by Rui *et al.* reported in the issue of February 2002 of Haematologica.[7]

However, as often occurs in all aspects of experimental and clinical medicine (and, unfortunately, human life) there is no, or little, direct interplay between hopes and reality. In all instances, before analyzing some strategic possibilities of manipulating cell division cycle in order to treat human cancers, it is necessary to consider some points.

First, cell division cycling is a process which involves *all* cells of the body, and its manipulation might be very harmful for normal cells in that it could cause catastrophic side effects.

Second, the mechanisms regulating the transition between a phase and the following one are very tightly controlled, and it is enormously difficult to restore a physiologic condition.

Third, our knowledge on the molecular mechanisms of cell cycling are still incomplete and any intervention to a single step of the process might alter the overall process causing unexpected damage. Nevertheless, even taking into account these considerations, the importance of developing new efficacious strategies for cancer therapy is so great that attempts must be made.

Two major avenues of intervention, which are not mutually exclusive but, conversely, reinforce each other, might be considered. One is pharmacologic, the other is genetic.

The first strategy is based on the use of molecules which, a) inhibit specific kinases/phosphatases required for specific cell cycles, or b) induce the expression of proteins which mimic those altered in neoplasias. The latter approach might now be pursued since there is a remarkable redundancy between proteins involved in cell cycle control.

The identification of highly selective enzyme inhibitors is, at present, difficult. Some identified inhibitors of Cdk and Chs 1 (kinases controlling essential steps of cell cycle), such as flavopiridol or UCN-01[8,9] are not completely specific and their effects are, at least in part, unpredictable. It will be important to obtain new compounds that inhibit cellular targets present uniquely in the tumor, for example STI571 that hampers only the activity of Bcr/Abl in chronic myelogenous leukemia.[10] The other side of the coin, i.e. modulators of gene transcription, are now available after the discovery that inhibitors of histone deacetylase are able to alter the nucleosomal structure and to induce gene expression. For example, butyric acid induces a rapid upregulation of $p21^{Cip1}$ (a powerful Cdk inhibitor) cell content by causing histone hyperacetylation and the subsequent transcriptional activation of the respective gene. The second strategy, the genetic one, relies on the possibility of transfecting malignant cells with one, or better more, cDNA encoding the cell division cycle protein(s) which are altered in cancer cells.

The major problems which must be overcome in trying to use the gene transfer approach in cancer treatment are: i) the strategy by which the cDNA can be introduced into the cells, ii) the percentage of cells into which the DNA is inserted, and iii) the choice of a method which allows stable integration of cDNA. Two major methods have been developed: the liposome strategy and the use of engineered viruses. In the former case the percentage of transfected cells is quite low, while the use of virus is made difficult by a number of potentially negative secondary effects. In all the instances, the possibility that all the malignant cells are transfected is low, particularly for solid tumors. Conversely, the manipulation of bone marrow (in an *ex vivo* condition, for example) for a subsequent autotransplantation is an idea to be pursued. At present, however, the available viruses cannot be efficiently transduced into hematopoietic cells.[11]

In conclusion, we do not believe that a single specific strategy, is now (or likely to be in the near future) the major route for efficacious treatment of human cancers. Gene therapy is certainly a promising approach, although some concerns about its efficacy (due also to technical problems) cast doubts on its applicability in the immediate future. However, its use along with new, highly specific drugs (e.g. STI571) and well-standardized therapies, raise considerable important hope that the devastating effects of a major cause of human death can be reduced.

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