Regulatory Genes and Drug Sensitivity

Kurt W. Kohn*

Many of the genes commonly associated with cancer participate in the regulation of cell proliferation and apoptosis. Alteration of these genes leads to molecular regulatory defects that are thought to drive the neoplastic process. But could the alterations also affect the response to chemotherapy? Hochhauser et al. (1) in this issue of the Journal address this question for the case of cyclin D1, a cell cycle regulator that is often expressed at higher than normal levels in breast cancer and other cancers.

The proteins of the cyclin D family stimulate cells to make a commitment to begin S phase (2). Cyclin D1 acts exclusively via the retinoblastoma protein (pRb) pathway of the network controlling the G1/S-phase transition; in the absence of pRb function, cyclin D1 appears to be dispensable (3).

Fig. 1 outlines the logic of this regulatory pathway, as currently understood. The effectors at the output are the E2F transcription factors that control a number of genes whose expression is required for cells to enter and complete S phase (i.e., S-phase genes), including the gene for dihydrofolate reductase (DHFR), which is the focus of the study by Hochhauser et al. (1), and thymidylate synthase, which was included in a previous study from the same laboratory (4). In addition, E2F can cooperate with the tumor suppressor protein p53 to stimulate apoptosis (5).

Many S-phase genes are stimulated by E2F and suppressed by E2F–pRb complexes. When pRb is nonfunctional or when cyclin D1 is expressed at higher than normal levels, elevated levels of S-phase gene products are also observed. Increased quantities of such products could, in principle, affect cellular sensitivity to chemotherapeutic drugs (i.e., chemosensitivity) in the following ways with diverse consequences: 1) If the overexpressed enzyme binds to or is the target of a drug, cellular sensitivity to that drug would usually be reduced [unless, as in the case of DNA topoisomerases (6), the drug–enzyme interaction yields a genotoxic product]; 2) if the overexpressed enzyme converts a drug from an inactive to an active form, cellular chemosensitivity could increase; and 3) overexpression of E2F-regulated genes would increase the fraction of cells in S phase and thereby could increase the effectiveness of antimetabolites, such as methotrexate, that selectively kill S-phase cells. A recent study by Stone et al. (7), for example, demonstrated that the induced expression of p16 (which abrogates cyclin D1 function; see Fig. 1) can arrest the cell cycle, prevent the commitment of cells to enter S phase, and thereby reduce cellular sensitivity to methotrexate. For antimetabolites, all of these mechanisms may operate to some degree. In addition, the overexpression of E2F may increase susceptibility to apoptosis (5) and, on this basis, could enhance chemosensitivity.

Enhanced expression of E2F can result from abrogation of pRb function or from overexpression of cyclin D1 (Fig. 1). In an earlier study, Li et al. (4) verified that cells lacking pRb function had higher than normal levels of DHFR and thymidylate synthase and found that these changes were associated with decreased cellular sensitivities to methotrexate and fluorodeoxyuridine. In the present and analogous study, Hochhauser et al. (1) transfected fibrosarcoma cells to overexpress cyclin D1 and found that increased levels of DHFR were associated with decreased sensitivity to methotrexate. Of the mechanisms listed above by which increased stimulation of E2F could affect chemosensitivity, the third mechanism presumably can be discounted, because both studies employed drug exposure times that were equivalent to one or more cell doubling times; as a result, even though the fraction of cells in S phase was increased, most cells would have had ample time to attempt S-phase entry. For methotrexate, measurements of drug and drug metabolite levels by Li et al. (4) excluded the second mechanism, which leaves the first mechanism as a plausible explanation. For base and nucleoside analogues, the situation could be more complex, because the enzymes required for conversion to the active phosphorylated products may also be E2F regulated. It is interesting that, in the current study (1), cells exhibited differences in sensitivity to cytarabine that were not consistently associated with levels of cyclin D1 expression, suggesting that multiple mechanisms may be at work.

The effects on chemosensitivity resulting from abnormal expression of regulatory genes thus can be complex and even contradictory because of opposing influences. Opposing influences also appear in the case of p53, whose expression can arrest cells at the G1/S-phase boundary and enhance DNA repair, thereby enhancing the ability of cells to survive DNA damage, but which can also stimulate apoptosis, thereby reducing survival [recently reviewed in (8,9)]. Accordingly, disruption of p53 has...
been reported to increase or decrease DNA-damage sensitivity in a variety of cell and tumor model systems (10-14).

Since clinical tumors, in principle, could be characterized in terms of a molecular diagnosis, so as to determine the molecular abnormalities driving the particular neoplastic process, therapy could potentially be selected accordingly (15). In light of the rapidly accumulating information from which one can begin to build a detailed understanding of the integrated functions governing cell proliferation and cell death, cancer therapies that are not only molecularly targeted but that are also customized to take into account the delicate balance of opposing influences described above may be realized in the future.

References

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