A wide variety of genetic and epigenetic factors have been implicated as determinants of anticancer drug resistance. Some of these are listed in Table 1. The growing body of published information regarding the function of oncogenes, tumor suppressor genes, cell cycle checkpoints, intracellular signaling cascades, and mechanisms of apoptotic cell death is shifting the focus of research toward microenvironmental and epigenetic factors. In this issue of the Journal, Taylor et al. (1) add significantly to the knowledge of epigenetic factors by documenting the effect of some microenvironmental factors as regulators of proteins involved in control of apoptosis following exposure to etoposide.

The phenomenon of drug resistance was recognized very early in the history of cancer chemotherapy. About 50 years have elapsed since the initial publications of the phenomenon (2–5). The heritable nature of the drug-resistant phenotype in transplantable mouse leukemia models, together with the rapidly emerging understanding of the biochemical mechanism of action of certain antimetabolites, contributed toward a tendency of early investigators to focus on genetic features of tumor cells as the determinants of drug sensitivity and resistance. This focus has contributed to some of the most dramatic discoveries in genetics and cell biology.

Studies of methotrexate resistance (6) revealed the phenomenon of gene amplification. Homogeneous staining regions in chromosomes present in drug-resistant cell populations were explained by amplification of dihydrofolate reductase genes. The demonstration that the somatic cell could undergo a change in gene copy number was contrary to the once-prevailing dogma of one gene–one polypeptide and helped revolutionize thinking about control of gene expression. Perhaps equally dramatic was the discovery of the phenomenon of multidrug resistance (7) and of the operation of p-glycoprotein as a membrane efflux pump that could reduce intracellular drug accumulation and thereby confer resistance to a broad range of structurally and mechanistically diverse drugs (8). Cloning and characterization of the MDR-1 gene encoding p-glycoprotein (9) provided impetus for investigation of tumor cell genetic factors in drug resistance, such as the multidrug resistance-associated MRP gene (10). Immunocytochemical studies of expression of multidrug resistance-associated proteins (11), together with in vitro drug sensitivity data, have supported the concurrent operation of multiple drug resistance mechanisms within one tumor cell population. Furthermore, immunocytochemical studies of clinical samples (12) have demonstrated associations between expression of some multidrug resistance-associated proteins and clinical drug resistance.

However, the tumor microenvironment may also play a key role as a determinant of drug response. This is well illustrated by studies that reveal a difference in tumor cell response to drugs that are assayed in monolayer versus spheroid culture (13). The spheroid model has been shown to represent tissues that form cell–cell junctions and to invoke signaling cascades, which may be important features of the in vivo, and, hence, the clinical, microenvironment. Indeed, relatively anoxic cells in the interior of spheroids have been shown to elaborate vascular endothelial growth factor (14). Anoxic conditions have long been known to reduce tumor cell sensitivity to radiation and radiomimetic drugs (15) and now have been shown to modulate apoptotic cell death in a setting in which angiogenesis is inhibited (16). Alterations of the interaction of tumor cells with the extracellular matrix can result in activation of signal transduction cascades, which can affect tumor cell response to drugs in an epigenetic manner (17).

In their article, Taylor et al. (1) demonstrate that microenvironmental factors can regulate molecules involved in control of apoptotic cell death following exposure to etoposide. The researchers suggest that the observed survival-promoting mechanisms can act “to prevent drug-induced cell death resulting in pleiotropic drug resistance.” Certainly, many other anticancer drugs are known to produce DNA damage and induce apoptosis, and it seems likely that the existence of epigenetic resistance mechanisms will prove to be a phenomenon of importance in cancer chemotherapy. The present article complements their previous work, which showed that microenvironmental factors within the germinal center act with Bcl-2 expression in reducing clinical drug resistance.

Table 1. Factors determining drug resistance

<table>
<thead>
<tr>
<th>Evidence for tumor cell genetic factors in drug resistance</th>
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<tbody>
<tr>
<td>• Drug resistance selected in experimental models can be heritable.</td>
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<tr>
<td>• Well-characterized mutations observed in tumor cells can confer resistance to specific drugs or drug classes or can confer multidrug resistance.</td>
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<tr>
<td>• Expression of drug resistance markers is sometimes associated with clinical drug resistance.</td>
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<tr>
<td>• Isolated, cultured tumor cells sometimes show in vitro drug resistance, corresponding to clinical drug resistance.</td>
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</table>

<table>
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<tr>
<th>Evidence for microenvironmental and epigenetic factors in drug resistance</th>
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</thead>
<tbody>
<tr>
<td>• Sensitivity of tumor cells to drugs in vitro can vary, depending on mode of assay (monolayer versus spheroids).</td>
</tr>
<tr>
<td>• Hypoxia modulates the DNA damage caused by radiomimetic drugs.</td>
</tr>
<tr>
<td>• Some forms of drug resistance that are selected for in vivo are only manifested in vitro when testing is performed on spheroids.</td>
</tr>
<tr>
<td>• Apoptotic cell death and angiogenesis are affected by hypoxia.</td>
</tr>
<tr>
<td>• Interactions of tumor cells with the extracellular matrix can modulate intracellular signaling and apoptotic cell death.</td>
</tr>
<tr>
<td>• Expression of molecules involved in the regulation of apoptotic cell death can be modulated by microenvironmental factors.</td>
</tr>
</tbody>
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Genetic and Epigenetic Factors in Anticancer Drug Resistance
apoptotic cell death among and increasing clonogenic growth of
dendritic cell death among and increasing clonogenic growth of
lymphoma cells (18). Thus, a mechanistic basis for the operation
of pharmacologic sanctuary sites for tumor cells could include
both the presence of microenvironmental factors that suppress
apoptosis—resulting in pleiotropic drug resistance—as well as
factors that limit the development of effective drug concentra-
tions in cells sequestered within particular three-dimensional
tumor masses. In such a scenario, the sequestered cells may also
bear genetic changes conferring drug resistance.

The emerging information regarding epigenetic and microen-
vironmental factors in drug resistance should be considered in
the broader context of tumor biology with the well-known ca-
veats of tumor cell heterogeneity and genetic instability. In ad-
dition, the patient’s genotype can potentially play an important
role in resistance or sensitivity to a given treatment. For ex-
ample, constitutional abnormalities in tumor suppressor gene
function, such as those that occur in familial retinoblastoma,
may modulate aspects of tumor cell response to chemotherapeu-
tic drugs. Future advances in chemotherapy can build on this
growing body of information to identify molecular targets that
can be exploited for new drug discovery initiatives and to design
more effective therapeutic regimens for existing drugs.

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