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In This Issue

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Cancer cells require gap junctions to metastasize (See article on pages 1189–1197.) Despite intensive interest in the genetic abnormalities of cancer cells, changes in gene expression that accompany later stages of tumorigenesis have attracted relatively little attention. Ito et al. have previously used subtractive libraries to clone genes that are differentially expressed between two mouse melanoma cell lines, one of which, BL6, can metastasize efficiently to the lungs when implanted subcutaneously, while the other subline, F10, cannot. Because both sublines metastasize when injected intravenously, their primary phenotypic difference probably relates to an early event in metastasis, such as detachment or intravasation. Now the authors show that the connexin gene CX26 is specifically expressed in BL6 cells but that expression of exogenous Cx26 allows F10 cells to metastasize. Conversely, point mutants in CX26 diminish the metastatic potential of BL6 cells and block their ability to transfer dye to endothelial cells in a coculture assay for gap junction activity. Although gap junctions typically form between cells bearing the same connexin proteins, Cx26 does not form gap junctions between BL6 cells. Furthermore, this connexin is not found in the endothelial cells that interact with BL6 cells. Ito and colleagues suggest that another endothelial connexin, possibly Cx43, forms heterotypic gap junctions with Cx26. The nature of the intercellular communication between the cell types and […]

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By John Ashkenas, Science Editor

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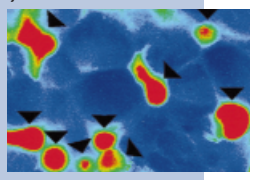

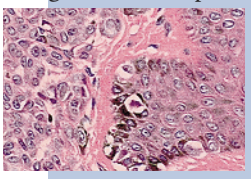

Despite intensive interest in the genetic abnormalities of cancer cells, changes in gene expression that accompany later stages of tumorigenesis have attracted relatively little attention. Ito et al. have previously used subtractive libraries to clone genes that are differentially expressed between two mouse melanoma cell lines, one of which, BL6, can metastasize efficiently to the lungs when implanted subcutaneously, while the other subline, F10, cannot. Because both sublines metastasize when injected intravenously, their primary phenotypic difference probably relates to an early event in metastasis, such as detachment or intravasation. Now the authors show that the connexin gene *CX26* is specifically expressed in BL6 cells but that expression of exogenous Cx26 allows F10 cells to metastasize. Conversely, point mutants in *CX26* diminish the metastatic potential of BL6 cells and block their ability to transfer dye to endothelial cells in a coculture assay for gap junction activity. Although gap junctions typically form between cells bearing the same connexin proteins, Cx26 does not form gap junctions between BL6 cells. Furthermore, this connexin is not found in the endothelial cells that interact with BL6 cells. Ito and colleagues suggest that another endothelial connexin, possibly Cx43, forms heterotypic gap junctions with Cx26. The nature of the intercellular communication between the cell types and its relevance to metastasis remain to be explored.

Effective arginine homeostasis in chronic renal failure

(See article on pages 1217–1225.)

Lau and coworkers have used isotopic tracer studies to follow the fate of arginine and its precursors and metabolic derivatives in vivo. De novo synthesis of arginine from citrulline is believed to occur primarily in the kidney, but the authors show that individuals undergoing hemodialysis (HD) for end stage renal disease (ESRD) are not arginine-deficient but maintain slightly elevated rates of arginine biosynthesis and roughly normal levels of plasma arginine. These findings confirm previous studies of rats in chronic renal failure and suggest that unidentified homeostatic mechanisms are at work. Lau et al. find evidence for at least two such mechanisms in ESRD patients: the suppression of oxidative breakdown of arginine and the elevation of plasma citrulline, which seems to be the limiting factor in normal arginine biosynthesis. Because these changes correlate with a dramatic increase in the conversion of arginine to the bioactive molecule nitric oxide (NO), they may shed light on endothelial dysfunction in ESRD patients. However, since the present findings with respect to NO metabolism are at odds with some other studies, Lau et al. suggest that NO production varies in different forms of ESRD and is sensitive to treatment by HD.

Mutant p53 protein induces drug resistance

(See article on pages 1261–1267.)

The tumor suppressor gene *p53* is mutated in roughly half of all cancers, but outright silencing of p53 expression is found in only a subset of these tumors. Prostatic carcinomas often express structurally altered p53, and Sullivan et al. have previously noted that advanced tumors from this tissue accumulate mutant p53 protein in parallel with the multidrug resistance protein MRP1. To probe the relationship between p53 expression and multidrug resistance, Sullivan et al. have now introduced a temperature-sensitive mutant of p53 into a prostate cancer cell line that expresses a normal form of the endogenous p53. Because this cell line also carries high levels of Bcl-2, it is protected from the proapoptotic effects of p53 overexpression, and the authors confirm that the mutant protein has the expected effects on the cell cycle. Thus, at the permissive temperature, the normally folded exogenous p53 prevents transfected cells from entering S-phase, but when the temperature is raised and the protein loses its ability to bind its cognate DNA sequence, the cells cycle normally. However, the structurally abnormal p53 that accumulates at the nonpermissive temperature is far from biologically inert: MRP, induced as a function of time after shifting cells to the nonpermissive temperature, allows these cells — but not transfected cells at the permissive temperature or parental cells at either temperature — to transport a specific ligand of MRP1 and to survive in high concentrations of cytotoxic drugs. The authors suggest that this effect of the partially unfolded p53 represents a specific derepression of the *MRP1* gene, whose promoter binds to, and is silenced by, wild-type p53. Alternatively, the constitutive expression of misfolded p53 may dominantly activate MRP1 expression, independent of any effect on endogenous p53. Regardless of the mechanism, these findings suggest that structurally abnormal forms of p53 can make cancer cells refractory to chemotherapy by driving the expression of drug resistance proteins.