Editorial

The role of cytoplasmic signal transduction pathways contributing to cell transformation and cancer is a generally accepted concept. The involvement of tyrosine kinase–encoded growth factor receptors and Ras in many cancers is unequivocal. Hyperexpression and/or mutation of the EGF receptor (erbB1) and Neu (erbB2) in combination with the establishment of autocrine/paracrine loops for their ligands (EGF, TGFα, heregulin, etc.) has been found in many cancers of epithelial origin. Frequent ras mutations in some of these malignancies also contribute to the transformed phenotype. EGF receptors regulate a host of signal transduction pathways involving Ras, phosphatidylinositol 3-kinase, phospholipase Cγ, protein tyrosine phosphatases, and Src tyrosine kinases. Ras, the activation of which is controlled by tyrosine kinases, in turn regulates signal transduction pathways including the mitogen-activated protein kinase (MAPK) pathway (MAPK is also referred to as extracellular response kinase, ERK) (1, 2).

The MAPK isoforms of 42 and 44 kD are expressed in most if not all human cell types. Specific substrates for MAPK include the cytoskeletal proteins MAP-2 and Tau, additional protein kinases including Rsk90 and MAPKAP2, cytoplasmic phospholipase A2 (cPLA2), and a host of transcription factors including Elk-1, c-Fos, ATF-2, and potentially c-Myc and c-Jun. Thus, activation of the MAPK pathway leads to a dramatic recruitment and activation of a large group of cellular regulatory processes, the potential generation of arachidonic acid metabolites including prostaglandins and leukotrienes, and altered gene expression. Activation of the MAPK pathway has been shown to be sufficient to transform NIH3T3 cells (3) and it has been generally believed that activated MAPK contributes to the transformed phenotype in many cancers.

Despite the large volume of work done on the regulation of the MAPK pathway related to cell growth and transformation, there is little substantive evidence in human tumors that the MAPK pathway contributes to malignancy. In this issue of the *Journal* is the paper by Sivaraman et al. entitled "Hyperexpression of mitogen-activated protein kinase in human breast cancer." In many ways the results in this paper have been anxiously awaited by many in cancer research. The authors report that the activity and expression of MAPK is significantly activated in carcinoma of the breast but not benign conditions including fibroadenoma and fibrocystic disease. Malignant epithelial cells in the breast and metastatic cells in lymph nodes demonstrated activated and hyperexpressed MAPK. The multiple approaches to show constitutive phosphorylation of MAPK that correlates with its activation and immunochemistry showing its hyperexpression strongly support the belief that activated and amplified MAPK expression can contribute to initiation and metastatic potential of breast cancer.

The hyperexpression of MAPK would allow strong signaling and override of compensatory regulatory phosphatases involved in reversing MAPK activation. Combined with amplification and autocrine/paracrine stimulation of the EGF/Neu growth factor receptors, a scenario is established that could contribute to a constitutively activated MAPK pathway. Now that hyperexpression and activation of MAPK has been found in human breast cancer, several questions must be addressed. First, can inhibition of MAPK influence the growth and metastasis of breast cancer cells. The recent development of inhibitors for MAPK kinase (MEK-1), the immediate upstream activator of MAPK, may prove useful in the treatment of breast cancer (5, 6). Combined with other treatments, including neutralizing EGF receptor/Neu antibodies, the inhibition of MAPK might prove therapeutically useful. A possible protection against apoptosis by MAPK might also be ablated by inhibition of MAPK activity (7). Second, the molecular basis for MAPK hyperexpression must be addressed to determine if this is causal or an effect of the malignant phenotype. Genetic strategies should be relatively straightforward to determine if there are rearrangements or mutations in the MAPK genes that might account for the hyperexpression in carcinoma of the breast. Third, the possible hyperexpression and activation of MAPK in other human tumors of epithelial origin must be screened to see if this is a frequent phenotypic consequence in carcinomas.

The last point, whether hyperexpression and activation of MAPK is a general phenotypic consequence in carcinomas, is extremely important. Certainly, cell lines established from carcinomas of several tissue origins do not have hyperexpression and activation of MAPK. Of course, it is possible that establishment of cell lines selects for carcinomas that do not have this phenotype or that it is lost during establishment. Little is known about these possibilities. What is certain is that the results reported by Sivaraman et al. (4) will be rapidly scrutinized, analyzed, and evaluated in many cancer research laboratories. This is an extremely exciting finding that has the potential of identifying an important therapeutic target. Given the advances being made with farnesyl transferase inhibitors as anticancer drugs by inhibiting Ras functions (8, 9), it is possible that disruption of signal pathways at the level of receptor tyrosine kinase, Ras, and the downstream MAPK could prove extremely effective in inhibiting cancer cell growth. We should have to wait only a short time to find the generality and potential therapeutic usefulness of the findings on hyperexpression and activation of MAPK in breast cancer to other carcinomas.

Gary L. Johnson
Director, Program in Molecular Signal Transduction
Division of Basic Sciences
National Jewish Medical and Research Center

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