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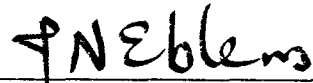
BIOCHEMICAL PATTERN-TARGETED ANTICANCER DRUG TREATMENT

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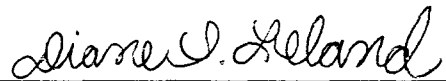
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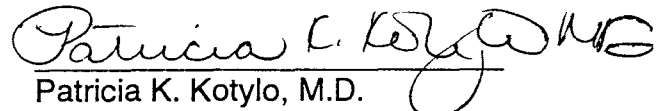
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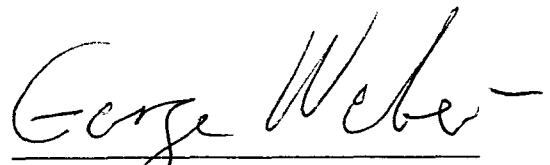
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ABSTRACT

1-Phosphatidylinositol 4-kinase (PI kinase) and 1-phosphatidylinositol 4-phosphate 5-kinase (PIP kinase) are the first two committed enzymes in the phosphorylation sequence of phosphatidylinositol, leading to the production of two second messengers, inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol. We tested the hypothesis that the increase of IP₃ concentration in hepatomas is due to an upregulation of PI and PIP kinase activities and that the kinase activities might be linked with malignant transformation and progression.

Through kinetic studies, standard isotopic methods were developed for measuring the enzymic activities in the particulate extracts. PI and PIP kinase activities were elevated in hepatomas of slow and intermediate growth rates (5.3- to 7.6-fold and 3.3- to 9.7-fold, respectively) and in rapidly growing rat hepatoma 3924A (28.5- and 45-fold, respectively) as compared to those of normal liver. In rat tissues of high cell renewal capacities (thymus, bone marrow, spleen, and testis), kinase activities were 5.6- to 8.4-fold and 4.3- to 6.3-fold, respectively, higher than in the liver. The steady-state activities of these kinases were elevated in human breast and ovarian carcinoma cells as compared to their normal tissue and cell counterparts. When rat hepatoma, human breast and ovarian carcinoma cells were plated in flasks, kinase activities steadily increased to a peak in mid-log phase. Tiazofurin injection in rats reduced kinase activities and IP₃ concentration in bone marrow with $t_{1/2}$ of 82, 78, and 23 min, respectively. In breast and

ovarian carcinoma cells, quercetin decreased PI kinase activity and IP₃ concentration in a dose- and time-dependent fashion and inhibited cell proliferation.

We tested the hypothesis that drugs that either acted on distinct biochemical targets or attacked different cell cycle phases would yield additivity or synergism. Synergistic interactions were obtained when quercetin or tiazofurin were combined with carboxyamidotriazole and when quercetin was given first, followed 12 h later by taxol. Synergism was evident when tiazofurin and taxol were given sequentially *in vitro* and *in vivo*.

The results indicate that the kinase activities are transformation- and progression-linked and may well be sensitive targets for new chemotherapeutic agents. The synergisms from drug combinations may be of interest in clinical trials for breast and ovarian carcinomas.

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