Advances in management of malignancies

Glutathione S-transferases and S-glutathionylation in cancer
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The glutathione-S-transferase (GST) super family comprises multiple isozymes with evidence of functional polymorphic variations. Over the last two decades, a body of data has accumulated linking aberrant expression of GST isozymes with the development and expression of resistance to cancer drugs. In particular, GST Pi (GSTP) is over-expressed in a number of different tumors compared to normal tissues (including ovarian, non-small cell lung, breast, colon, liver, pancreas and lymphoma). Moreover, a significant range of anticancer drugs can cause an increased expression of GSTP in drug resistant selected cell lines (and drug treated patients). From a functional viewpoint, not all drugs used to select for resistance are substrates for catalysis by GSTP. In fact, catalytic constants for GSTP conjugation reactions with virtually all standard cancer drugs are poor. So why is GSTP so frequently over-expressed in these situations? There is recent evidence that GST isozymes, and GSTP in particular, have multiple functions in cells, many unrelated to thioether bond catalysis with chemical moieties. These include: (1) ligand biding and transport of heme, bilirubin, nitric oxide; (2) protein: protein interactions with possible chaperone like functions; (3) regulation of mitogen activated protein kinases, particularly c-jun NH2 terminal kinase (JNK); (4) mediation of the for-ward reaction of the post-translational process of S-glutathionylation. Of these, aberrant kinase signaling pathways and altered protein S-glutathionylation patterns are both characteristic of the malignant phenotype. What happens in the absence of GSTP? GSTP null animals have essentially normal development and life spans. Mouse embryo fibroblast (MEF) cells isolated from wild type or GSTP null animals differ in a number of characteristics related to signaling and growth. For example, the doubling time for wild type cells is 33.6 h compared to 26.2 h for GSTP null. Both early passage and immortalized MEF cells from GSTP null animals express significantly elevated activities of extracel-lular regulated kinases (ERK1/ERK2). Null animals had constitutively elevated c-jun NH2-terminal kinase (JNK) activity compared to wild type and this is correlated with altered regulation of genes downstream of JNK. As a whole, the genetic absence of GSTP influences the capacity of stress kinases to regulate gene expression and this can have an impact on proliferation pathways. The non-lethality of the deletion points to possible functional redundancy and implies that other GST (or other redox proteins) may substitute for the absence of GSTP. Cysteine residues in proteins provide a nucleophilic site for a number of disparate post-translational modifications. For example, disul-fide bonds between vicinal thiols have major implications for three dimensional protein structures. Contingent upon the steric properties and local environment of the cysteine, lipidation of these residues may occur through S-isoprenylation, S-farnesylation, S-geranylgeranylation or S-palmitoylation. The direct addition of GS- to cysteines with low pKa’s creates an S-glutathionylated residue, resulting in an increase in both molecular weight (of 605) and negative charge (from the glutamic acid residue). GSTP facilitates the forward reaction and glutaredoxin, sulfiredoxin or thioreredoxin can contribute to the reverse reaction. The reversible nature of this cycle is important in facilitating a sulfur based regulatory pathway that can expedite re-sponse to stress conditions. Importantly, a number of phosphatases can be regulated by S-glutathionylation and this provides a link and conduit with phosphate based signaling pathways. Because the structure, function and cell distribution of proteins can be affected by S-glutathionylation, the importance of GSTP in mediating this reac-tion could have significant consequences and may be a contributory factor in the high expression levels of GSTP in many tumors. These multiple functionalities contribute to the recent rational efforts to tar-get GSTP with novel small molecule therapeutics. While the ultimate success of these attempts remains to be shown in the clinic, at least three drugs are in late-stage clinical testing. Two of these (NOV-002 and Telintra) are being tested therapeutically as small molecule mye-loproliferative agents. As the field progresses, the concept of designing new drugs that might interfere with protein:protein interactions between GSTs and regulatory kinases provides a novel approach to identify new targets in the search for cancer therapeutics.

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NOV-002, a glutathione disulfide mimetic, is a pleiotropic modulator of cellular redox balance
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NOV-002 is a novel formulation of oxidized glutathione (GSSG) currently in Phase 3 clinical trial in advanced non-small