Complex formation between metabolic enzymes in tumor cells: Unfolding the MDR1-IDE paradigm

To the Editor:

We greatly appreciated the recent article by Orina and colleagues (1) reporting on progress in identifying novel modulators of multidrug resistance (MDR). However, we think that, in addition to profiling ATP-binding cassette (ABC) transporter gene expression toward improved anticancer drug development (1), protein-protein interactions involved in MDR should also be vigorously investigated in order to appropriately address this major clinical challenge. In this context, we have reevaluated a previously published study that had predicted a physical interaction between MDR1/P-glycoprotein (P-gp), a major cellular ATPase, and insulin-degrading enzyme (IDE), whereby this proposed dimer was assumed to contribute to the growth factor-mediated unresponsiveness of carcinomas to antineoplastic treatment (2).

Interestingly, we have now found in three different human tumor cell lines, specifically the A549 non-small cell lung (adenocarcinoma), the MCF-7 breast cancer, and the HepG2 hepatoma cell lines, evidence for a complex formation between MDR1/P-gp and IDE (Fig. 1). These results are consistent not only with the data of the above-mentioned bioinformatic study (2), but also with a more recently elaborated putative tumor suppressor role of IDE that is possibly counteracted by MDR1/P-gp through displacement of intracellular growth stimulators such as insulin and/or nuclear factor kappa-B (NF-κB) from their IDE binding sites (3).

Given that further analysis has now equally revealed that MDR1/P-gp harbors an LXCXE-like amino acid motif, more precisely the LXFXE motif used by the Tax viral oncoprotein for the binding of the retinoblastoma tumor suppressor protein (RB) along with the latter’s targeting for proteasomal degradation (4), it is also conceivable that MDR1/P-gp contributes to oncogenesis in a Tax-like manner by leading not only to RB’s proteolysis, but also to IDE’s digestion and ensuing inactivation by the proteasomal machinery. This scenario is supported by the proven association of MDR1/P-gp with subunits of the proteasome (5).

Taken together, our work communicated here constitutes the first experimental demonstration of the anticipated MDR1-IDE heterodimer (2, 3), which thus provides a lead for significantly expanding current efforts to further understand and modulate MDR (1). It should therefore be worthwhile to further explore this presumably important new avenue in patient-derived tissue samples and, moreover, as a basis for the development of novel anticancer drugs that target directly drug resistance mechanisms.

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References

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