

B2 The role of polyamine catabolism in antitumor drug response.
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The interest in polyamine catabolism has increased since it has been directly associated with the cytotoxic response of multiple tumor types to exposure to specific antitumor polyamine analogues. Human polyamine catabolism was considered to be a two-step pathway regulated by the rate-limiting spermidine/spermine N1-acetyltransferase (SSAT) that provides substrate for an acetyl polyamine oxidase (APAO). However, we have recently cloned a variably spliced, human polyamine oxidase (PAO) that is both inducible by specific polyamine analogues and efficiently uses unacetylated spermine as a substrate, demonstrating an additional enzyme that significantly contributes to polyamine homeostasis and drug response. Most importantly, human PAO is induced by specific polyamine analogues, typified by N1-ethyl-N11[(cyclopropyl)methyl]-4,8-diazaundecane (CPENSpm), in a tumor phenotype specific manner in cell lines representative of the major forms of solid tumors, including lung, breast, colon, and prostate. The sensitivity to these antitumor polyamines analogues can be significantly reduced if the tumor cells are co-treated with 250 uM of the PAO inhibitor, N1,N4-bis(2,3-butadienyl)-1,4-butanediamine (MDL 72,527), suggesting that the H₂O₂ produced by PAO plays a direct role in the observed cytotoxicity. These results strongly implicate PAO as a new target that may be exploited for therapeutic advantage.