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MOLECULAR MEDICINE IN PRACTICE

Next Generation Sequencing of Prostate Cancer from a Patient Identifies a Deficiency of Methylthioadenosine Phosphorylase, an Exploitable Tumor Target

The EGFR T790M Mutation in Acquired Resistance to an Irreversible Second-Generation EGFR Inhibitor
Youngwook Kim, Jeonghun Ko, ZhengYun Cui, Amir Abolhoda, Jin Seok Ahn, Sai-Hong Ou, Myung-Ju Ahn, and Keunchil Park

ABOUT THE COVER

The uracil-metabolizing enzyme dUTPase is a key component of de novo thymidine nucleotide biosynthesis and its expression is tightly regulated in replicating tissues such as the follicular germinal centers of human palatine tonsil (pictured). However, dUTPase is frequently overexpressed in human cancers and this has been firmly linked to drug resistance to chemotherapeutic agents that target thymidylate synthase (TS). Using immunohistochemistry and quantitative RT-PCR, evidence of dUTPase overexpression in a cohort of non-small cell lung cancers (NSCLC) was observed. Small interfering RNA-mediated gene silencing of dUTPase induced a strong synthetic lethal effect in NSCLC cell lines to two class-specific TS-targeted therapies including pemetrexed and fluorodeoxyuridine. Inhibition of dUTPase represents a promising, mechanism-based therapeutic approach to significantly enhance the efficacy of TS-targeted chemotherapeutic agents by overcoming a critical drug resistance pathway. For details, see article by Wilson and colleagues on page 616.