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Abstract 3568: CYP3A4 epoxygenase activity mediates ER+ mammary tumor growth and angiogenesis, in part, through EET biosynthesis and is inhibited by biguanides

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While cytochrome P450 enzymes (CYPs) are implicated in tumor angiogenesis through biosynthesis of epoxyeicosatrienoic acids (EETs), little is known about breast cancer cell-intrinsic CYPs that exhibit epoxygenase activity, such as CYP3A4. In an orthotopic breast cancer model, silencing of epithelial CYP3A4 suppressed angiogenesis-related escape of ER+ breast tumors from dormancy. While the diabetes drug metformin inhibits mitochondrial complex I and inhibits tumor growth, how it does so is unknown. Metformin inhibited CYP epoxygenase activity and co-crystallized in the active site of CYP3A4, hydrogen bonding with arginine 212, allowing the development of hexyl-benzyl-biguanide (HBB) as a CYP3A4 inhibitor using molecular modeling. HBB exhibited more than 10-fold greater potency than metformin for inhibition of ER+ mammary tumor growth and inhibited associated tumor angiogenesis. HBB inhibited EET biosynthesis ~40-fold more potently than metformin and was ~40-fold more potent for activation of AMPK phosphorylation. EETs suppressed and CYP silencing promoted AMPK phosphorylation, linking CYPs with AMPK regulation in breast cancer. HBB depolarized mitochondria, reduced oxygen consumption rates and suppressed the Warburg effect, while EETs restored the mitochondrial membrane potential. CYP3A4 silencing and HBB treatment increased reactive oxygen species (ROS) production, suggesting that CYPs suppress cancer cell death, in part, through suppression of ROS. CYP3A4 silencing sensitized breast cancer cells to hormonal therapy and chemotherapy, abrogated by EETs. Because EETs are autocrine, paracrine and endocrine, these results implicate CYPs in tumor growth, in part, through cell-cell mediation of mitochondrial homeostasis and demonstrate the potential of CYP3A4 as a therapeutic target in breast cancer.