Interrogating SGK3 Function in Cancer

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PI3K signaling regulates cell cycle progression, growth, and survival and is dysregulated in many cancers, including the majority of breast cancers. Activated PI3K transduces signals to AGC kinases of which Protein Kinase B isoforms (AKT1, AKT2, AKT3) are best characterized in cancer. SGK kinases are also AGC kinases with 55% structural homology to AKT and SGK3 showed increased activity in PIK3CA-mutated breast cancer cells with low-AKT dependence. To further understand the functions of SGK3 in PIK3CA-mutated cancers, SGK3, AKT, and downstream substrate activation were studied using western blot under different conditions of PI3K pathway inhibition. AKT and mTOR inhibition promoted initial downregulation of SGK3 T320 phosphorylation followed by hyperinduction of its phosphorylation at later timepoints. By contrast, PI3K inhibition led to initial downregulation without hyperinduction. To understand the function of induced SGK3, SGK3 function was downregulated using ATP-competitive SGK inhibition, ATP-competitive PDK1 inhibition, or SGK3 knockdown to identify potential substrates of SGK3. GSK650394 and GSK2334470 respectively may be useful for rapid SGK3 inhibition in order to better understand its functions. In addition, the present findings implicate NDRG1, NEDD4L, mTORC1, PRAS40, and GSK3? as downstream SGK3 effectors in a novel SGK3-dependent, AKT-independent signaling pathway in downstream PI3K signaling and the rescue of PIK3CA-mutated breast tumors from AKT inhibition.

Awards Won:

Intel ISEF Best of Category Award of $5,000

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