Department of Pharmacological Sciences

Key Roles for the Lipid Signaling Enzyme Phospholipase D1 in the Tumor Microenvironment During Tumor Angiogenesis and Metastasis
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Description

We are working on varied cancer projects centered on a signal transduction pathway that we have long-standing expertise in. Our lab cloned the genes for the Phospholipase D (PLD) superfamily in the mid to late 1990's and have explored their cell biological and now physiological roles since. Current projects using knockout mice for each allele have revealed roles for the PLD1 isoform in the tumor environment (Chen et al, attached) in angiogenesis and metastasis, and we have been able to phenocopy the suppression of cancer progression in the knock-out animals using a small molecule inhibitor we've been developing. One current project involves extending this work specifically to breast cancer, by crossing genetic mouse breast cancer models into our knockout strains and assessing the consequences on cancer progression. We are also examining the mechanisms underlying the requirement for the PLD1 signaling pathway in the metastasis step, which appears to involve inhibition of a step performed by platelets in the dissemination process. Both PLD1 and PLD2 may have roles in the tumor cells as well as in the tumor environment (e.g. Hif1a induction, VEGF secretion), which is being examined using the genetic cancer models.

Independently, both of the PLD1 and PLD2 isoforms play supporting roles in immune responses and lipid handling physiologically. One recent finding is that PLD1-/- and PLD2-/- mice on a high fat diet are largely protected from the high level of fat accumulation seen in the liver in obese wild-type mice. Since obesity and chronic inflammation are strong predisposers for hepatocellular carcinoma (HCC), this raises the issue of whether the PLD knockout animals will be resistant to the development of HCC, and we are now designing the experiments to test that.