PURDUE UNIVERSITY | Department of Industrial and Physical Pharmacy

Industrial & Physical Pharmacy Seminar

IPPH 69600

Monday, August 28, 2023
3:30 PM in RHPH 164

"Role of the Gut Microbiota-Aryl Hydrocarbon Receptor Axis in Colorectal Cancer Progression"

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First Seminar

The gut microbiota has emerged as an essential contributor to host health and disease. It produces thousands of metabolites that can impact host physiology beneficially or pathologically. However, the identities and biological activities of the majority of gut bacterial metabolites remain largely unknown. Aryl hydrocarbon receptor (AhR) is a ligand-activated host transcriptional factor that can bind structurally diverse groups of chemicals. AhR regulates the expression of genes involved in multiple physiological processes including xenobiotic metabolism. We hypothesized that AhR can sense previously unknown gut bacterial metabolites and mediate host-gut microbiota interaction. To test this hypothesis, we screened a collection of 118 gut bacteria for AhR activation using a luciferase-based AhR-reporter system in HepG2 cells. *Fusobacterium nucleatum* (*Fn*) exhibited the highest activation, and from its culture extracts, we identified three metabolites fusotrisindoline (FTIN), trisindoline (TIN), and streptindole (STIN) as AhR activators through activity-guided fractionation and structure elucidation. Cell-based ligand competition assay revealed that these metabolites directly bind to AhR, with FTIN being the most potent AhR activator. Given that *Fn* is enriched in colorectal cancer (CRC) tissues, we investigated whether these *Fn* AhR-activating metabolites play a role in CRC progression. We found that while wild-type *Fn* promotes the CRC cell (H508) proliferation, a *Fn* deletion mutant that does not produce AhR-activating metabolites can not. Altogether, we have identified novel AhR-activating metabolites previously unknown to be produced by Fn and revealed that Fn promotes CRC progression via AhR activation. Based on these findings, we plan (1) to investigate how these *Fn* metabolites mediate CRC progression through the AhR pathway both *in vitro* and *in vivo* and (2) to determine whether Fn-producing AhR-activating metabolites can be detected in clinical CRC tissues.