Recrutement pHD

EQUIPE

Intitulé: Heme, Ubiquitin and Lung Cancer
Chef(s) d'équipe ou responsable(s) scientifique(s) de plateforme
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SUJET DE THESE PROPOSE et PI DU SUJET

Titre: Mechanisms of lung tumorigenesis driven by heme signaling and protein degradation machinery
PI du sujet (Nom, Prénom) : LIGNITTO, Luca

RESUME DU PROJET

Heme is a ubiquitous prosthetic group associated with numerous hemoproteins, such as hemoglobin. In addition to its role as a cofactor, recent evidence demonstrated that heme works as a signaling molecule which regulates different pathways and functions, including mitochondrial respiration and transcription. Among the functions controlled by signaling heme, particularly relevant to our research it is the ability of heme to control protein degradation via the Ubiquitin-Proteasome System, which is the major cellular pathway regulating protein turn-over. Indeed, it has been shown that binding of heme to several protein, including p53, is able to promote their ubiquitination and proteasomal-dependent degradation. Interestingly, to date, despite increasing research efforts aimed to decipher the biological roles of the heme signaling, little is known about the mechanisms underlying the heme-regulated protein degradation, and how alteration of this pathway contributes to disease. In our laboratory, we are interested in understanding the fundamental processes regulating the heme-regulated protein destruction and uncovering how deregulation of this pathway in cancer contributes to the mechanisms of tumorigenesis. Specifically, we focus our studies on Non-Small Cell Lung Cancers (NSCLCs), which is the major subtype of lung cancer and one of the most aggressive and lethal solid tumors. Therapeutic options and outcomes for NSCLCs patients have remained virtually unchanged over the past thirty years.

PROJECT OVERVIEW

Recently, we have discovered that Loss-of-Function (LOF) mutations of the tumor suppressor KEAP1, which are present in ~20% of NSCLCs patients, promote cancer progression by disrupting the heme signaling homeostasis. In particular, we discovered that LOF mutations of KEAP1 promote metastasis formation in NSCLCs by inhibiting the heme-regulated degradation of the pro-metastatic transcription factor BACH1 (Lignitto, L. et al. 2019). Mechanistically, we uncovered that heme triggers the degradation of BACH1 by promoting its binding to the ubiquitin ligase FBXO22, which in turn ubiquitylates BACH1 triggering its proteasomal-dependent destruction. Using mouse models of lung cancer, we found that genetic knock-out of FBXO22 promotes metastasis formation by increasing the levels of BACH1, whereas pharmacological stimulation of the heme-FBXO22 system suppresses metastasis formation by promoting the degradation of BACH1 (Lignitto, L. et al. 2019). Altogether, our research provides critical insights into the fundamental mechanisms governing the heme-regulated protein degradation and reveals that FBXO22 functions as a “heme-sensor” ubiquitin ligase, capable of coupling protein degradation with variations of the heme signal. Furthermore, our work identifies the KEAP1-heme-FBXO22 system as a novel tumor suppressor pathway in NSCLCs and indicates that drugs targeting the heme-FBXO22 pathway represent an effective therapeutic strategy to inhibit NSCLCs progression.

The goal of this project is to discover the molecular mechanisms regulating the heme-FBXO22 pathway, to identify its targets, and to determine their role in lung cancer pathogenesis. The results of this study will be determinant to identify specific cancer vulnerabilities driven by alteration of the heme pathway that could be exploited for the design of new and more effective therapies to be used in the clinic.

Being a multidisciplinary laboratory, for this project we will use orthogonal approaches that will leverage biochemical (e.g., western blot, immuno-purification) and cellular/molecular biology (e.g., PCR, qPCR, confocal microscopy) tools, together with proteomics (e.g., quantitative mass spectrometry) and mouse genetics (e.g., genetically engineered mouse models in combination with in vivo CRISPR/Cas9 strategies to inactivate any gene-of-interest)

PUBLICATION:

FINANCEMENT (à remplir par le chef d’équipe/responsable Plateforme)

Funding ANR JC 36 months. Starting January 1st 2022