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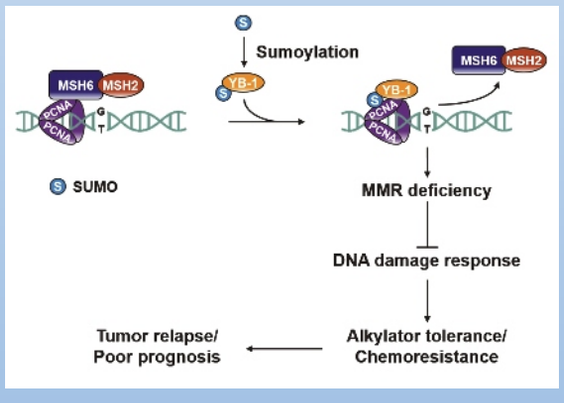
研究興趣

麥如村老師的研究目標是探討引發癌症的分子機制，並藉以發展新型抗癌策略。主要的研究標的是具有DNA/RNA結合能力的YB-1 (Y-box binding protein-1)，以及具有RNA解螺旋酶(helicase)活性的DDX3，其中YB-1在許多癌症已被證實為一致癌因子(oncogene)，DDX3則在肝癌為一腫瘤抑制因子(tumor suppressor)。我們藉由分析它們與微核醣核酸(microRNA)、DNA修補機制(DNA repair)、以及蛋白質轉譯後修飾(protein post-translational modification)的交互作用，發現YB-1和DDX3除了參與調節多樣性的細胞功能之外，在癌症發生過程中也扮演重要角色。本實驗室以生化與分生方法於體外細胞實驗中驗證，並結合動物實驗，利用這些研究成果設計新型癌症治療策略。

• YB-1的小泛素轉譯後修飾在腫瘤產生抗藥性過程中扮演重要功能

YB-1廣泛參與調控細胞內的許多生物過程，而細胞可能演化出多重機制來調節YB-1在這些不同生物過程中的活性。生物醫學界多年的研究成果提供強而有力的證據，指出YB-1在細胞內的反常表現與「癌症標誌(Hallmarks of Cancer)」的發生有關，這些發現支持YB-1在癌症產生過程中的主要角色。本實驗室發現，YB-1的小泛素轉譯後修飾(Sumoylation)在其抑制DNA錯配位修補系統時扮演功能性角色。由於錯配位修補系統的缺失直接導致基因突變的累積以及DNA損傷反應訊息傳遞路徑的失活，探究YB-1的小泛素化修飾在錯配位修補系統缺失中的作用，不僅可增進我們對YB-1在腫瘤細胞中導致基因組不穩定性和產生甲基化藥物耐受性的理解，同時亦可提供設計防止癌症病患預後不良治療策略時的重要指引。



• DDX3調控外泌體生成之機制及其治療肝癌之潛力

肝癌是全球癌症相關死亡的第二大原因，即使在切除腫瘤的手術後，肝癌患者的5年存活率也很低，術後復發率高達70%。肝癌難以治癒的原因，在於其對常用化療藥物容易產生抗藥性而導致高復發率。外泌體(exosome)為細胞外囊泡(extracellular vesicle)的一種，直徑介於30-150奈米，外層為雙層脂膜包裹細胞內的小分子物質如蛋白及核酸等，其參與許多重要細胞功能、與多種疾病發生有關，具有早期診斷疾病、並可作為載體治療疾病之潛力。研究發現，癌症細胞利用分泌外泌體除可能作為早期的生物標記(biomarker)外，亦與腫瘤發生、轉移、抗藥性有關。因此，瞭解造成癌症發生過程中細胞外泌體生成異常的因子及機制，可發展成為用來診斷癌症的生物標記、作為癌症治療的潛力標的。本實驗室發現在肝癌中為腫瘤抑制因子(tumor suppressor)的RNA解螺旋酶DDX3，具有調控外泌體外泌及內容物組成之潛力，我們期望能發現DDX3抑制肝癌之新機轉，以應用於臨床肝癌早期

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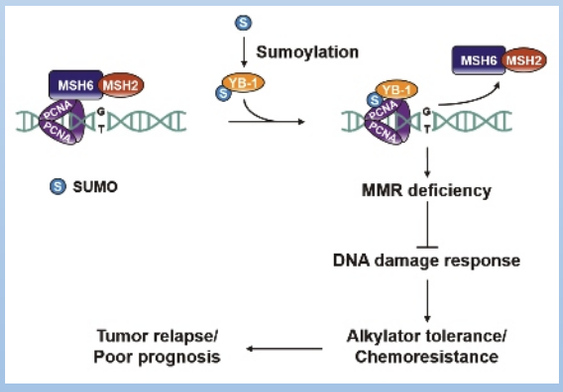
Research Interests

The research goal of Dr. Ru-Tsun Mai's laboratory is to explore molecular mechanisms that involve in tumorigenesis and to develop new anti-cancer strategy. The main research targets are YB-1 (Y-box binding protein-1), a DNA/RNA binding protein, and DDX3, an RNA helicase. Among them, it has been confirmed that YB-1 is an oncogene in various cancers and DDX3 is a tumor suppressor in liver cancer. By analyzing their interactions with microRNAs, DNA repair systems, and protein post-translational modifications, we found that YB-1 and DDX3 are involved in the regulation of diverse cellular functions and play important roles during the development of cancer. Apart from biochemical and molecular biological studies, we validate research results with animal experiments to design new cancer treatment strategies.

• YB-1 sumoylation in DNA mismatch repair-related chemoresistance

YB-1 participates in the regulation of a wide spectrum of cellular processes. For these diverse functions, cells may evolve various mechanisms to regulate biological activities of YB-1. Evidences provided by extensively studies strongly support that the de-regulation of YB-1 plays a master role in cancer biology, which contributes to all of the "Hallmarks of Cancer". Previously, we found that post-translational modification of YB-1 by SUMOs



plays a functional role in inhibiting DNA mismatch repair system. As MMR deficiency directly leads to mutation accumulation and DNA damage response signaling inactivation, delineating the role of YB-1 sumoylation in MMR deficiency will certainly not only advance our understanding of YB-1-induced genome instability and alkylator tolerance in cancer cells, but also provide insight into design of therapeutic strategies that prevent patients from an unfavorable prognosis outcome.

• Roles of DDX3 in regulating exosome biogenesis and its therapeutic potential on HCC

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide. Even after curative surgery, the five-year survival rate of HCC patients is low, and the post-operative recurrence is as high as 70%. Reports suggest that HCC is difficult to cure for its chemoresistance to commonly used chemotherapeutic agents. Exosome is a kind of extracellular vesicles with 30-150 nm in diameter, the outer layer is a lipid membrane encapsulating small molecular substances such as proteins and nucleic acids. It plays pivotal roles in numerous cell functions and the occurrence of diseases including cancer, thereby serving as diagnostic biomarkers and new treatment targets of diseases. Studies indicated that exosomes secreted by cancer cells are associated with tumorigenesis, metastasis, and drug resistance. Therefore, understanding factors involved in the de-regulation of extracellular secretion during tumorigenesis can be developed into biomarkers for diagnosing cancer and as potential targets for treating cancer. Recently, we found that RNA helicase DDX3 plays potential roles in regulating exosome biogenesis. These results will be informative for new mechanisms on DDX3-mediated inhibition of HCC and ultimate development of early diagnostic and novel therapeutic strategies for liver cancer.