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研究興趣

• 肺癌轉譯醫學相關研究

肺癌在全世界及台灣都是癌症相關死因排名第一的癌症種類。雖然十多年來數代標靶藥物及免疫療法的開發，搭配傳統化/放療已經能夠有效延長病人的存活，然全球肺癌患者平均五年存活率仍不到20%，且抗藥性腫瘤的復發始終是無解的難題。本實驗室於肺癌的研究包括對癌細胞中的「幹細胞特性」（stemness property）之探討，以及免疫療法相關研究。

a. 開發針對幹細胞因子BMI1之小分子藥物：本實驗室與生技中心合作開發之小分子藥物BI-44已申請多國專利(PCT / Us2018 / 030300)且獲得Janssen-Taiwan 2019補助，向臨床試驗推進。

b. 發現兩個新穎基因BAZ1B與RBMXL1會出現在DNA複製時的replication fork上。抑制此二基因會造成replication fork stalling，使DNA受到損傷並釋出碎裂的單股/雙股DNA在細胞質，引起強烈的干擾素反應（IFN response）與細胞死亡。我們已篩檢出了一個能結合並抑制BAZ1B與RBMXL1的前驅化合物。由這種藥物引起的肺癌細胞死亡會伴隨強烈的干擾素反應並提高對後續免疫療法的敏感度。

c. 發現重要的胚胎幹細胞因子OCT4在不同的肺癌種類中有不同的異構型。在鱗狀細胞肺癌中，我們發現OCT4 mRNA與文獻中已知的結構完全不同，因保留了intron而表現出一個全新的蛋白質(簡稱ORF1)。ORF1會調控另一個幹細胞因子SOX2的表現，若抑制ORF1則會造成癌細胞死亡。我們已經證實ORF1 會出現在近70%的肺癌臨床樣本中，並對其分子機制作進一步研究。

• 慢性肺部疾病相關研究

慢性阻塞性肺病(簡稱COPD)與特發性肺纖維化(簡稱IPF)皆為重大公共健康問題，並且隨著人口老化與環境污染，其發生率不斷提昇。COPD目前為全球第三大死因，而IPF的五年存活率僅20%，目前醫學上對兩種疾病都尚無有效藥物或治療方式。本實驗室發現，以基因投遞或小分子藥物誘導肺泡細胞的重編程（reprogramming）使其產生幹細胞特性，在小鼠模式中能有效促進肺組織的修復並且對這兩種疾病的症狀產生實質療效。目前正在進行專利的申請，往臨床試驗推進，並且也再進一步探討其重編程之詳細分子機制，以及與免疫細胞間的交互作用。*本研究成果亦獲得科技部 "2019未來科技突破獎" 肯定。*

• 新穎癌症治療技術之開發：歐傑分子治療（Auger Molecular Therapy）

歐傑效應（Auger Effect）的產生是源自原子內層電子軌域（K層或L層）出現空缺(vacancy)時，外層電子往內遞補並因能階位差伴隨放出特性輻射，此輻射能量q在原子中會轉移至其他外層電子而將其彈射出原子外。被彈射出的電子稱為歐傑電子（Auger Electron），而整個過程則稱為歐傑效應。歐傑電子能量僅數十至數百eV，射程大約 1 至 10 nm，但其 LET（linear energy transfer）卻能高達 100 **keV**/ μ m，因此若Y能控制歐傑效應發生在癌細胞的 DNA中，預期將能造成大量qDNA雙股斷裂、造成細胞老化或死亡。

本實驗室與NanoRay Biotech公司產學合作開發的歐傑分子治療，是以獨特的專利技術設計的穿透式X光管，能產生特性輻射，與重原子（例如碘）的K-edge能量匹配而高效率的產出歐傑電子，對癌細胞造成嚴重的DNA損傷，並且能以較低的劑量即獲得與傳統X-ray相當的腫瘤抑制效果。目前歐傑分子治療已經向美國FDA提出IND申請，並可望於明年展開臨床第一期試驗。

此外由於歐傑效應會對癌細胞DNA產生強烈的損傷，歐傑治療後的癌細胞不論細胞質或exosome中所含的碎裂單/雙股DNA均遠高於傳統放射治療，引發強烈的干擾素反應與免疫反應。未來我們將繼續研究歐傑治療搭配免疫療法的原理及可行性。

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Research Interests

• Translational Medical Research in Lung Cancer

Lung cancer is the leading cause of cancer-related mortality worldwide as well as in Taiwan. Drug resistance and highly-metastatic activity are the major reasons of treatment failure and account for most lung cancer death. Although the development of target therapy and immune check-point therapy have successfully improved the survival in subpopulations of lung cancer patients, recurrence invariably occur, and the overall 5-year survival rate remains <20%. Our translational research focused on the stemness property and immunotherapy in lung cancer.

a. Development of small-molecular BMI1 inhibitor: In collaboration with Development Center for Biotechnology, the novel anti-cancer drug BI-44 has been developed and patented (PCT/US2018/030300), which is also granted by Janssen-Taiwan 2019 for clinical translation.

b. Tow novel genes, BAZ1B and RBMXL1 were identified, which function on the replication fork of DNA. Knockdown of these genes induces replication stalling, leading to DNA damage and accumulation of ssDNA/dsDNA in cytosol, which elicit intensive interferon responses. A novel lead structure binding to and inhibiting BAZ1B and RBMXL1 has been identified, which kills cancer cells and sensitizes tumors to host immune response.

c. A novel isoform of embryonic stemness factor OCT4 was identified in lung squamous-cell carcinoma (LSCC). The OCT4 RNA in LSCC retains all the introns and thus encodes a novel protein (indicated as ORF1 here) that has never been reported in literatures. ORF1 regulates SOX2 (another key embryonic stemness factor) expression. Knockdown of ORF1 leads to the inhibition of SOX2 expression and cell death. We have also identified the expression of ORF1 in nearly 70% of LSCC patient samples. Detailed molecular functions of ORF1 are under investigation.

• Therapeutic Approach to Chronic Lung Diseases

Chronic obstructive pulmonary disease (COPD) and Idiopathic pulmonary fibrosis (IPF) are both major public health problems with a high and growing prevalence. COPD is currently the third most common specific cause of death globally, and IPF has a five-year survival rate <20%. Unfortunately, no pharmaceutical approach to date can control or restore the degenerated pulmonary functions induced by the 2 diseases.

Our lab found that reprogramming of endogenous alveolar epithelial cells (AECs) via stemness factor BMI1, either through nanoparticle-mediated gene delivery or by small-molecule agonists, showed promising results that significantly improved lung functions in mouse model of both disease. The clinical translation and the study of detailed molecular mechanisms of the reprogramming are ongoing. *These studies are also awarded by "Future Tech 2019" of Ministry of Science and Technology.*

• Novel Cancer Therapy Approach: Auger Molecular Therapy

Auger effect is a physical phenomenon that creation of an initial inner atomic shell vacancy leads to a series of electron transitions, accompanied by the emission of characteristic X-Rays and so-called Auger electrons. Most of these Auger electrons have an energy around 20 - 500 eV and a travel distance from 1 - 10 nm in biological matter. When occured on DNA, Auger effect can induce violent DNA damages and cell death. Auger effect thus has been a topic of considerable interest in radiotherapy of cancer.

In collaboration with NanoRay Biotech, a novel transmission type X-Ray tube was developed, which produce characteristic photons that can efficiently induce Auger effect in combination with specific heavy atoms that have corresponding K-edge energy (e.g. 33 keV NanoRay with Iodine). Auger Molecular Therapy (AMT) can induce superior anti-tumor effect comparing to conventional radiotherapy. AMT has been subjected to IND application in US FDA, and is supposed to entery Phase 1 study in 2020.

Furthermore, since AMT induces violent DNA damages, the fragmented ssDNA/dsDNA exposed cytosol and exosome are much larger than conventional radiotherapy, which elicits intensive interferon and host immune responses. The potential combination of AMT with immunotherapy and the detailed molecular mechanisms are under investigation.