Number 32, 2013.10.01

臺灣大學「發育生物學與再生醫學研究中心」電子報

Research Center for Developmental Biology and Regenerative Medicine Newsletter

中心網頁：http://homepage.ntu.edu.tw/~ntucdbrm622/

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本次主題

1. 活動消息
   聽數學與生命對話-9/28-12/21
   國立台灣大學科學教育發展中心

2. **2013/10/5-6日-國際幹細胞與型態發育學術研討會**
   Professor Andrew McMahon
   2013/10/7日
   Professor Irma Thesleff-台大牙醫所
   Professor Yang Chai-台大牙醫所
   Professor Min-Huey Chen-台大牙醫所

3. 專題演講預告
   Genome regulation in cell fate control and plasticity
   2013年11月 04日
   Howard Y. Chang, M.D., Ph.D.
   Stanford University School of Medicine
   Howard Hughes Medical Institute

4. 專題演講摘要

   Transcription factor Foxm1 in lung development and cancer
   王翊青老師/清華大學生物科技所

國立臺灣大學科學教育發展中心
Center for the Advancement of Science Education

關於【聽數學與生命對話】系列講座

進入二十一世紀，爭奪科學聖杯的領域，逐漸從二十世紀獲得許多重大突破的物理學，轉向仍然充滿未解之謎讓人興奮不已的生命科學！但唯一不變的是，獨立於人類經驗之外的數學，都是這兩個領域的根基與發展關鍵！

但作為純粹抽象代表的數學，是如何與實質存在的生物相遇呢？讓人類思想的產物，看似全然脫離現實應用的質數研究為天平的一端，而質樸如液胞形狀與表面張力及幾何的相關性為天平的另一端，我們將各自出發，來回的跳躍逼近，去尋找數學在大自然生態系、個別生命科學與醫學研究各方面，是如何緊密相關和發揮作用。

臺灣大學、師範大學、清華大學與中央研究院的教授與研究員們，將揭開看似飄渺虛無，不食人間煙火的頂尖數學研究，從質數研究、貝索方程、統計與數值分析、到微分與黎曼幾何等，一次次抽象與實質存在的碰撞，將激起我們最遼闊無邊的想像。

歐幾里得 幾何之父
西元前三世紀的希臘數學家

系列講座內容

09/28(六) 數學是發現，還是發明？
臺灣師範大學數學系 **洪萬生**教授

10/12(六) 探索內心的小宇宙：談大腦的理論與模型
清華大學生命科學系 **羅中泉**教授

10/26(六) 生物離子通道的數學建模
臺灣大學應用數學科學研究所 **林太家**教授

11/02(六) 從細胞世界看微分幾何
臺灣師範大學數學系 **林俊吉**教授

11/16(六) 解密孟德爾：機率與基因定位
中央研究院生物醫學科學研究所 **范盛娟**研究員

11/23(六) 醫學中的數學偵探
臺灣大學流行病學與預防醫學研究所 **陳秀熙**教授

12/07(六) 現實生活的模擬農場：漫談生態系中的族群數量變化
中央研究院統計科學研究所 **劉維中**助研究員

12/21(六) 醫學影像中的數學
成功大學數學系/雲嘉南區域數學資源中心 微積分動畫計 畫主持人 **舒宇宸**助理教授

活動預告

2013 國際幹細胞與形態發育學術研討會 暨 第九屆臺灣幹細胞學會年會

International Symposium on Development, Morphogenesis and Stem Cells & 9th Annual Meeting of Taiwan Society for Stem Cell Research


Cheng-Ming Chuong


David M Gardiner


Jonathan Slack


Irma Thesleff


Shigeru Kondo


Andrew McMahon


Ken Muneoka


Malcom Maden

Date: Oct. 5th-6th, 2013

Location: Longevity Hall, Taipei Veterans General Hospital, Taipei, Taiwan

國外講員 (Confirmed International Speakers):

Prof. Cheng-Ming Chuong / University of Southern California / USA
Prof. David Gardiner / University of California, Irvine / USA
Prof. Jonathan Slack / University of Minnesota / USA
Prof. Irma Thesleff / University of Helsinki / Finland
Prof. Shigeru Kondo / Osaka University / Japan
Prof. Andrew McMahon / University of Southern California / USA
Prof. Ken Muneoka / Tulane University / USA
Prof. Malcolm Maden / University of Florida / USA

國內講員 (Confirmed Domestic Speakers):

王仰高(Yang-Kao Wang) / 臺北醫學大學
吳金洌(Jen-Leih Wu) / 中央研究院
吳益群(Yi-Chun Wu) / 國立臺灣大學
林泰元(Thai-Yen Ling) / 國立臺灣大學
林頌然(Jerry Lin) / 國立臺灣大學
洪士杰(Shih-Chieh Hung) / 國立陽明大學
郭漢岑(Jean-Cheng Kuo) / 國立陽明大學
彭貴春(Guey-Chuen Perng) / 國立成功大學
游正博(John Yu) / 長庚醫院/中央研究院
楊良棟(Liang-Tung Yang) / 國家衛生研究院
蔡金吾(Jin-Wu Tsai) / 國立陽明大學
薛一蘋(Yi-Ping Hsueh) / 中央研究院
顏伶汝(Lin-Ju Yen) / 國家衛生研究院

Submit an abstract now!

Please complete the on-line registration and send your abstract (Word file only) to abstractsubmission@tsscr.org.tw before Aug. 30th, 2013.

報名請洽 臺灣幹細胞學會 Taiwan Society for Stem Cell Research
Address: Rm. B111, United Medical Building, No.250, Wuxing St., Xinyi Dist., Taipei City 110, Taiwan
Tel: 886-2-2736-1661 ext 3283
Email: tsscr2010@gmail.com
Web : http://www.tsscr.org.tw

請使用條碼掃描器掃描右方QR-Code碼可直接登入學會網站-活動訊息網報名參加!

主辦單位：• 臺灣幹細胞學會 •國立陽明大學 • 台北榮民總醫院

協辦單位：• 國立臺灣大學發育生物學與再生醫學研究中心 • 國立成功大學醫學院傷口再生與修復中心 • 國立中興大學畜產預測化與基因體研究中心

• 教育部教育部「精準醫學及產學人才培育先導型計畫」教學資源中心 • 國科會生物處幹細胞及再生醫學研究計畫辦公室 • 國科會生物處生科研究推動中心

指導單位：•國立陽明大學 •教育部構可與頂尖大學計畫

Professor Andrew McMahon
Director & Professor
Eli and Edythe Broad Center for
Regenerative Medicine and Stem Cell

Andrew P. McMahon, Ph.D., is director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC. He is Provost Professor and the inaugural holder of the W. M. Keck Professorship of Stem Cell Biology and Regenerative Medicine. In addition, he chairs the newly created Department of Stem Cell Biology and Regenerative Medicine at the Keck School.

McMahon and his team study the mechanisms that underlie the assembly, repair, and regeneration of critical organ systems, and have made enormous contributions to the understanding of the way the kidney matures during development. In building knowledge on these subjects, they seek to provide an informed, logic-based platform for translating basic research into practical applications in the area of regenerative medicine. This carries enormous potential for the treatment of human disease, as stem cell science offers a particularly broad reach. It can provide insights into normal and abnormal development in human cells, and holds the potential for the repair and replacement of human tissues and organs.
McMahon's basic research has yielded important findings into the biology of mammalian signaling factors that have been translated into clinical medicine with the development of a novel anti-cancer drug, vismodegib, the first FDA-approved hedgehog pathway inhibitor, in a Curis/Genentech partnership.

專題演講預告

時 間：2013年10月 07日　星期一
04:30PM~05:30PM

地 點： School of Dentistry
National Taiwan University
9W 405 (4th floor in the School of Dentistry)

時間	主題	主講人
16:00-16:30	Tooth Replacement and Dental Lamina	Professor Irma Thesleff
16:30-17:00	Molecular Regulation of Dental Root Development	Professor Yang Chai
17:00-17:30	Dynamic Investigation Model for Epithelial Invegination during Tooth Development	Professor Min-Huey Chen

Speaker 1: Professor Irma Thesleff

Professor and Research Director
Institute of Biotechnology
University of Helsinki Finland

Biosketch

Professor Irma Thesleff graduated from the Dental School of the University of Helsinki in 1972, received her PhD in 1975 on studies on the etiology of cleft lip and palate, and was a postdoctoral scientist at National Institute of Dental Research in Bethesda, USA 1978-79. She is a specialist in Orthodontics and was Professor and Chairman of the Department of Pedodontics and Orthodontics at the Institute of Dentistry, University of Helsinki, 1990-1995. Since 1996 she is the Research Director of the Developmental Biology Program at the Institute of Biotechnology, University of Helsinki. This program has gained the status of a Center of Excellence from the University as well as from the Academy of Finland. Her work has been recognized by many national and international awards including the Helsinki City Science Prize, Anders Jahre Prize in Medicine by the Oslo University, the Distinguished Scientist Award and Isaac Shour Memorial Award of IADR, and honorary doctorates in several universities. She is an invited member of the Finnish Academy of Science and Letters and EMBO and an AAAS Fellow.

Her research interest is the mechanisms of embryonic organ development. She is best known for work on tooth development and the model she presented on how sequential and reciprocal signaling between cells and tissues regulates the morphogenesis of teeth. Her group has developed mouse models and a variety of novel organ culture methods for examining the functions of signal molecules, and the research has expanded to include the development of bone and several organs developing as ectodermal appendages.

Speaker 2: Professor Yang Chai
Specialist in craniofacial development and birth defects
Professor and Director, Center For Craniofacial Molecular Biology
Associate Dean of Research
George and Mary Lou Boone Chair in Craniofacial Molecular Biology
Ostrow School of Dentistry of USC

Expertise
- **craniofacial developmental biology**
- **birth defects, including cleft palates**
- **cranial neural crest cells**
- **gene expression in development**
- **the management of oral infection**
- **human anatomy**

Additional Information
- **Fellow, American Association for the Advancement of Science**
- **Distinguished Scientist, International Association of Dental Research**

Speaker 3: Professor Min-Huey Chen
Professor, Graduate Institute, School of Dentistry, National Taiwan University
Director, Visiting Staff, Division of Esthetic Restoration, Department of Dentistry, National Taiwan University Hospital

Professional specialties
1.Restorative and Esthetic Dentistry
2.Stem Cell Research
3.Tissue Engineering
4.Biomaterials Development

Main Research Interests

Translational Medicine in Organogenesis
1.Epithelial-mesenchymal interactions in dental organogenesis
2.Neurogenesis in dental organogenesis
3.Mechanism of organogenesis in periodontal tissues

Stem Cells Tissue Regeneration
1.Cartilage Regeneration
2.Salivary Gland Regeneration
3.Tooth Regeneration

Development of Biomaterials
1.Development of dental nano composites (2 patents, 4 fileing)
2.Development of dental implant

Coordinators: School of Dentistry, National Taiwan University
Developmental Biology and Regeneration Center,
National Taiwan University

專題演講預告: 2013年 11月4日
演講時間:下午2:00分 醫學院202教室
演講題目:Genome regulation in cell fate control and plasticity

Howard Y. Chang, M.D., Ph.D.
(張元豪教授)
Stanford University School of Medicine
Howard Hughes Medical Institute

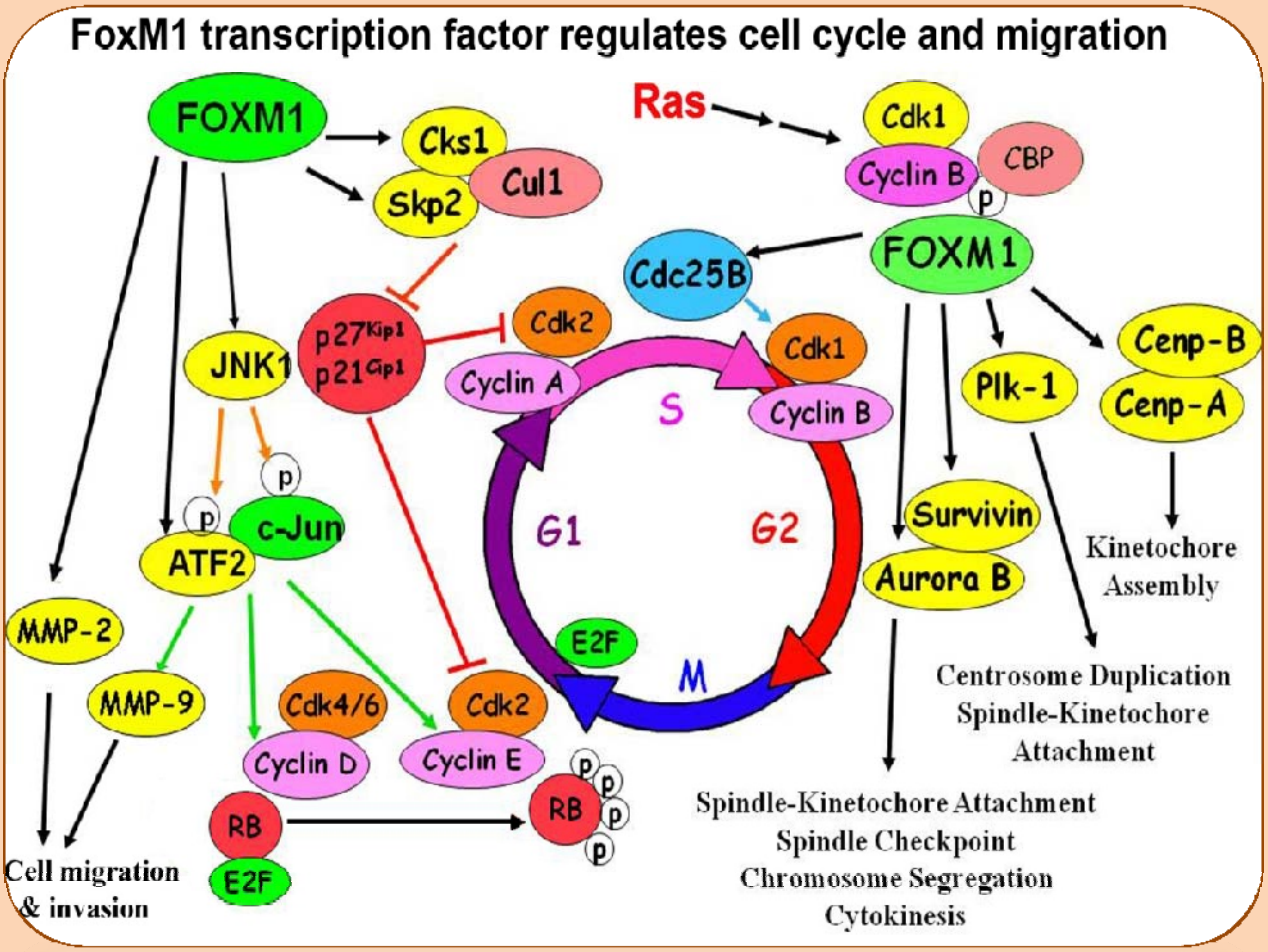
"DR. Howard Chang is from Taiwan but educated in US with MD from Harvard and PHD from MIT, mentored by Dr. David Baltimore. He did clinical training in Stanford dermatology. He is now a professor in Stanford University and junior investigator of Howard Hughes Medical Institute. Dr. Chang is distinguished for his pioneer work in long noncoding RNA, which is found to play important roles in epigenetic regulation during development, aging, cancer, etc. Dr. Chang will be in Taipei for Annual Conference of Asia Epigenome Alliance meeting. I am glad he is willing to visit our Research Center for Developmental Biology and Regenerative Medicine in Taiwan University and interact with our faculties. In addition to outstanding research, he is an inspiration to our young physician scientists and medical students. You can find more about him in http://changlab.stanford.edu "

by Cheng Ming Chuong

Transcription factor Foxm1 in lung development and cancer

清華大學生物科技所
王翊青老師

在哺乳類細胞中，有多達五十幾種**Forkhead box (Fox)** 基因轉錄因子家族蛋白。這些蛋白透過相似的氨基酸序列與基因**promoter DNA**結合，並參與調控細胞分裂、分化、細胞轉型癌化及老化等過程。其中，**Forkhead Box**家族中的成員**M1**亞型 **(FOXM1)** 蛋白表現於生長分裂中的細胞，並且調控細胞週期**G1/S** 與**G2/M**進程，以及相關基因的轉錄表現，這些基因包括有**JNK1, ATF2, DNA Topoisomerase IIa, Cks1, Skp2, Cdc25B, Plk-1, Aurora B** 及**CenpA/B/F**等等(圖一)。我們過去的研究中利用**RNAi**抑制細胞中**Foxm1**基因的表現量，會使細胞週期停滯在**G1**或**G2** 期，造成細胞分裂速度減緩，並且因胞質分裂缺失而產生**DNA**多倍體。若將小鼠胚胎成纖維母細胞**(MEFs)** 中的**Foxm1**基因利用**Cre-LoxP** 方式剔除後，除了會阻斷細胞分裂，且會引發$p27^{Kip1}$、$p21^{Cip1}$與**Ink4 locus**的 $p19^{ARF}$及$p16^{Ink4a}$等蛋白的表現量增加，促使培養中的正常細胞早衰進入老化。因此，我們認為細胞的複製與分裂需要**Foxm1**蛋白。


FoxM1 transcription factor regulates cell cycle and migration
FOXM1
Cks1
Skp2
Cul1
Ras
Cdk1
Cyclin B
CBP
p
FOXM1
Cdc25B
p27Kip1
p21Cip1
Cdk2
Cyclin A
JNK1
S
Cdk1
Cyclin B
Plk-1
Cenp-B
Cenp-A
p
p
c-Jun
ATF2
G1
G2
Survivin
Aurora B
Kinetochore
Assembly
MMP-2
MMP-9
E2F
M
Centrosome Duplication
Spindle-Kinetochore
Attachment
Cdk4/6
Cyclin D
Cdk2
Cyclin E
p
p
p
RB
RB
E2F
Spindle-Kinetochore Attachment
Spindle Checkpoint
Chromosome Segregation
Cytokinesis
Cell migration
& invasion

圖一

Foxm1與肺癌形成

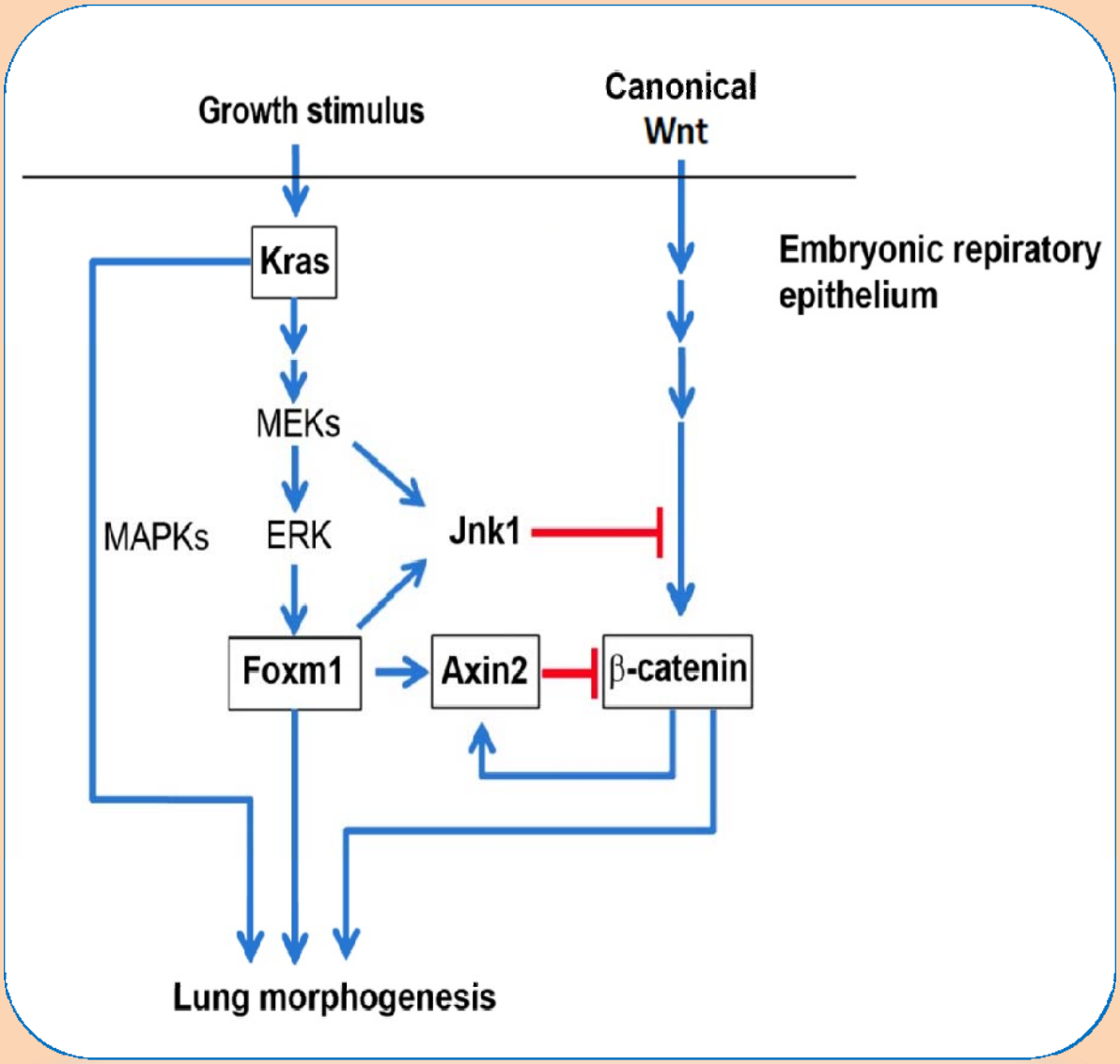
先前的研究指出諸多癌症中，如肝癌、肺癌、大腸直腸癌、胰臟癌、乳癌、卵巢癌等等，**Foxm1**表現量均大量增高，且與癌化程度呈現正相關。我們過去利用**SPC-rtTA/tetO-Cre/Foxm1$^{fl/fl}$**基因剔除小鼠結合癌症模式，發現從肺臟上皮細胞中剔除**Foxm1** 基因，可顯著地抑制**urethane** 或**MCA/BHT**誘發肺腺瘤。若改變腫瘤誘發的實驗程序，使**SPC-rtTA/tetO-Cre/Foxm1$^{fl/fl}$**小鼠先受到化學致癌物誘導形成肺腫瘤後，再誘發**Foxm1** 基因專一性剔除，同樣地可以減少肺腫瘤生長，因此推論在活體中，**Foxm1**為腫瘤起始及癌化進程所必需。

在臨床上，**10~30%**的人類非小細胞肺癌具有**Kras**基因點突變，而前述**urethane**致癌物所引發的小鼠肺臟腺瘤經分析後，約有半數也具有**Kras**基因獲得功能突變**(gain-of-function mutation)**，因此我們進一步運用**SPC-rtTA/tetO-Cre/tetO-Kras^{G21D}/Foxm1$^{fl/fl}$** 小鼠模式的初步研究顯示，**Foxm1**為致癌**Kras**訊號傳遞路徑的重要的下游，剔除**Foxm1**基因抑制**Kras^{G21D}**誘發腫瘤形成。我們另外利用基因轉殖模式，於**SPC-rtTA/tetO-Foxm1-ΔN**小鼠肺臟上皮細胞中表現活化態的**Foxm1**。肺臟上皮細胞層因此增生**(hyperplasia)**，但尚不足以引發腫瘤形成；但與致癌**Kras^{G12D}**轉殖基因共同表現時，**Foxm1**則會使**Kras^{G12D}**誘發的肺腫瘤快速生長。目前實驗室運用基因轉殖與基因剔除等小鼠動物模式，致力於了解活體中**Foxm1**蛋白在致癌基因**Kras**調控訊號傳遞路徑中的角色。同時發展以抑制癌細胞中**Foxm1**基因表現及蛋白活性控制癌細胞生長，希望成為將來治療癌症新策略的參考。

Foxm1與肺臟發育

在小鼠胚胎發育初期，將Foxm1基因進行全身性剔除，會造成小鼠成肝細胞及心肌細胞的分裂缺失，導致胚胎出現肝臟、心臟等器官發育缺失，造成死胎。我們發現 Foxm1 mRNA的表現量在小鼠肺臟發育早期的embryonic、pseudoglandular 及canalicular等階段均高，但隨著肺臟進入到成囊化(sacculation)時期，細胞的生長速度驟降，且Foxm1表現量只剩約5~10%，因此我們推測Foxm1與肺臟細胞生長與分化調控可能相關。我們於是將發育中的小鼠肺臟上皮細胞中誘發活化態的Foxm1表現(SPC-rtTA/tetO-Foxm1-ΔN)，發現胚胎肺臟上皮細胞增生並伴隨著肺臟成囊化缺失。此一肺臟成囊化缺失的現象與活化態的$Kras^{G12D}$轉殖基因(SPC-rtTA/tetO-$Kras^{G12D}$) 所造成的表現型類似。相反地，在SPC-rtTA/tetO-Kras ^{G12D}/TetO-Cre/$Foxm1^{fl/fl}$小鼠中剔除Foxm1基因，則可減緩由$Kras^{G12D}$ 造成的肺臟上皮層結構性缺失，再次證明Foxm1為Kras的重要下游調控因子。令我們感到意外的是條件式剔除Foxm1基因，小鼠胚胎肺臟上皮細胞仍然會複製分裂，這與肺癌細胞的反應明顯不同；有趣的是我們發現剔除Foxm1基因時，肺臟上皮細胞中另一與調控細胞分裂相關的Wnt訊號路徑則被活化，可能因此代償Foxm1缺失。

另一方面，是否Foxm1具有抑制canonical Wnt signaling的功能? 我們進而以SPC-rtTA/tetO-Foxm1/TOPGAL 小鼠模式實驗發現，當胚胎肺臟上皮轉殖表現Foxm1，則會抑制canonical Wnt reporter 的表現。透過 mRNA qRT-PCR 及 Chromatin Immunoprecipitation (ChIP) 分析，證明Foxm1蛋白可直接與Axin2及JNK1基因啟動子DNA 結合，並活化基因轉錄。已知Axin2蛋白會抑制β-catenine蛋白的穩定性，進而降低由β-catenine進入細胞核中進行基因轉錄調控。而JNK non-canonical訊號路徑，則會抑制canonical Wnt訊號路徑。同樣地，於SPC-rtTA/tetO-$Kras^{G12D}$/TOPGAL小鼠肺臟上皮細胞層表現活化的$Kras^{G12D}$，canonical Wnt也受到抑制。我們因此認為，胚胎發育時期肺臟上皮細胞中的Foxm1蛋白參與協調Kras 與 canonical Wnt訊號傳遞路線(圖二)，基因表現量需應受到精確的調控。


Growth stimulus
Canonical
Wnt
Kras
Embryonic repiratory
epithelium
MEKs
MAPKs
ERK
Jnk1
Foxm1
Axin2
β-catenin
Lung morphogenesis

圖二

分子遺傳實驗室簡介

王翊青老師自**2001**年進入美國伊利諾大學芝加哥分校就讀博士學位，研究基因轉錄因子**Forkhead Box M1 (FOXM1)**如何調控細胞週期與細胞生長癌化。**2006**年起分別在伊利諾大學芝加哥分校、芝加哥大學、辛辛那提兒童醫院醫學中心等單位繼續博士後研究，**2012**年**8**月進入清華大學生物科技所任職助理教授，教授小鼠模式生物醫學研究等課程，並運用基因轉殖與剔除小鼠動物模式，進行肺臟發育、損傷修補與肺癌等相關基礎研究。目前實驗室(圖三)專注於研究與細胞生長密切相關的**Foxm1**基因轉錄因子，希望了解**Foxm1**蛋白調控的下游基因網路在小鼠胚胎發育及細胞癌化過程中的角色。

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