DENG, Lih-Wen (鄧力文)

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ACADEMIC QUALIFICATION

Education

1992 - 1996	National Taiwan University	B. Sc.
1996 - 2000	University of Cambridge	Ph.D.
	(Advisor: Professor Richard N. Perham)	

Career History

2000 - 2002
Postdoctoral Research Fellow (Supervisor: Professor Jack Strominger)
Research Fellowships awarded from Juvenile Diabetes Research Foundation
Dept of Molecular and Cellular Biology, Harvard University

2002-2003
Postdoctoral Research Fellow (Supervisor: Professor Jack Strominger)
International Fellowships awarded from A*STAR, Singapore
Dept of Molecular and Cellular Biology, Harvard University

2004 – Present
Assistant Professor, Department of Biochemistry
National University of Singapore

RESEARCH

Our research aims to understand the molecular mechanisms of cancer development and to search for novel therapeutic targets. In the past few years, we focused on the investigation of the biological functions of a novel MLL/trithorax gene member, Mixed Lineage Leukemia-5 (MLL5) which is located at the locus frequently associated with myeloid malignancy. Emerging evidences suggest that MLL5 has important functions in hematopoiesis, chromatin regulation and cell cycle machinery network.

1. Role of MLL5 in cell cycle regulation

(a) Phosphorylation Mitotic regulatory: We demonstrated a cell cycle-dependent phosphorylation regulation of MLL5 by Cdc2, and showed that the mitotic phosphorylation of MLL5 regulates its sub-cellular distribution and is required for mitotic progression (Liu et al., 2010, JBC). It is the first report on the influence of phosphorylation modification of MLL family protein influences its cell cycle regulatory function. Since MLL protein family are involved in epigenetic regulation through the histone modification, this study also enlightens us to explore

the implication of such phosphorylation regulation on the potential histone methyltransferase activity of MLL5 in epigenetic control of the cell cycle.

(b) MLL5 as a novel negative regulator of p53: We have previously demonstrated that over-expression or knockdown of MLL5 leads to cell cycle arrest at both G_1/S and G_2/M phases (Deng et al., 2004 PNAS; Cheng et al., 2008; IJBCB). Recently, we demonstrated a new role of MLL5 as a cellular determinant of camptothecin, which degrades MLL5 in actively replicating cells and thereby stabilizes p53 through Ser392 phosphorylation (Cheng et al., 2011, accepted in Oncogene). Our findings shed light on a role of MLL5 in the antitumor activity of camptothecin, and provide novel insights into the regulation of tumor suppressor p53 by MLL5.

(c) MLL5 and genomic Instability: Most tumor cells are characterized by increased genomic instability and chromosome segregation defects, often associated with centrosome hyperamplification mitotic multipolarity. We found that knockdown of MLL5 resulted in multipolar spindles and cytokinesis defects. In addition, we identified that the central domain of MLL5 was able to interact with the mitotic kinase Plk1, a highly conserved Ser/Thr kinase that is required for bipolarity at cell division. Therefore, MLL5 may have important roles in mitotic centrosome formation, spindle integrity and genomic stability (Liu et al., 2011; in preparation for Current Biology).

2. Characterization of a novel isoform of MLL5 as a potential therapeutic target for cervical cancer.

Human papillomavirus (HPV) infection accounts for over 99% of cervical cancers, molecular-targeting therapy of cervical cancer with siRNA against HPV oncogenes E6 and E7 is viewed with hope. We have recently identified a novel MLL5 isoform being exclusively present in HPV16/18-positive cervical cancer cells. Interaction of MLL5β with AP-1 located in the long control region of HPV18, activates E6/E7 transcription. Knockdown of MLL5β down-regulates both E6 and E7 oncogenes, resulting in the p53 restoration and the reduction in Rb phosphorylation (Yew et al., 2011 submitted to EMBO J). So far, there are no published works linking MLL5 to the pathogenesis of cervical cancer. The finding described here will initiate a novel research direction for MLL5 in cancer biology, where it will provide potential therapy for cervical cancer treatment

3. Generation of Mll5 knockout animal model.

In order to confirm our cellular finding in a more physiological relevant system, we have established *Mll5*-deficient animal models. To begin with we generated a zebrafish system with the collaboration with Dr Vladimir Korzh (IMCB, Singapore) and Dr Yun-Jin Jiang (NHRI, Taiwan) to study MLL5 functions *in vivo*. We have found the developmental role of zebrafish Mll5 in myogenesis and photoreceptor formation. (Wang et al., 2011; Cheng et al., 2011, in preparation). In addition, we have generated the *Mll5* knockdown mice model. We constructed a targeting vector with loxP-flanked exons 4 of Mll5. Deletion of exon 4 results in a frame-shift mutation, leading to only a 55-amino acid truncated fragment (full-length: 1858 amino-acid). We have successfully generated both $Mll5^{+/-}$ and $Mll5^{-/-}$ mice and are examining their phenotypes.

In addition to our main research activity on biological functions of MLL5, we also participate in a multi-disciplinary collaborative research programme for the biological function of gasotransmitter, H_2S. We have demonstrated the structural and function of human cystathionine-gamma-lyase (CSE) on H_2S production (Sun et al., 2009, JBC; Huang et al., 2010, JMB). We are currently assessing the anti-proliferating effects of a slow-releasing H2S drug on various cancer cells and are investigating the molecular mechanism for the killing effects (Lee et al., 2011, submitted to Cancer Research)

PUBLICATION

Book Chapter

Tan MC & **Deng LW**. Chapter 3: Enzymology in "Microbial Biotechnology: Principles and Applications" Ed: Lee YK. 3rd Edition.

Research Papers

- Fanutti C, Del Pozzo G, De Berardinis P, Guardiola J, **Deng LW** & Perham RN. (1998) Phage-display of antigenic peptides applied to vaccine design. Biochem Soc Trans. 26(1):S8
- **Deng LW**, Malik P &Perham RN. (1999) Interaction of the globular domains of pIII protein of filamentous bacteriophage fd with the F-pilus of Escherichia coli. Virology. 253(2):271-277.
- **Deng LW** & Perham RN. (2002) Delineating the site of interaction on the pIII protein of filamentous bacteriophage fd with the F-pilus of Escherichia coli. J Mol Biol. 319(3):603-614
- Malik P, Klimovitsky P, **Deng LW**, Boyson JE & Strominger JL. (2002) Uniquely conformed peptide-containing beta 2-microglobulin-free heavy chains of HLA-B2705 on the cell surface. J Immunol. 169(8):4379-4387
- **Deng LW**, Chiu I & Strominger JL. (2004) MLL 5 protein forms intranuclear foci, and overexpression inhibits cell cycle progression. Proc Natl Acad Sci U S A. 101(3):757-762.
- Cheng F, Liu J, Zhou SH, Wang XN, Chew JF & **Deng LW**. (2008) RNA interference against mixed lineage leukemia 5 resulted in cell cycle arrest. Int J Biochem Cell Biol. 40(11):2472-2481.
- Sun Q, Collins R, Huang S, Holmberg-Schiavone L, Anand GS, Tan CH, van-den-Berg S, **Deng LW**, Moore PK, Karlberg T & Sivaraman J. (2009) Structural basis for the inhibition mechanism of human cystathionine gamma-lyase, an enzyme responsible for the production of H(2)S. J Biol Chem. 284(5):3076-3085.
- Huang S, Chua JH, Yew WS, Sivaraman J, Moore PK, Tan CH & **Deng LW**. (2010) Site-directed mutagenesis on human cystathionine-gamma-lyase reveals insights into the modulation of H2S production. J Mol Biol. 396(3):708-718.
- Liu J, Wang XN, Cheng F, Liou YC & **Deng LW**. (2010) Phosphorylation of mixed lineage leukemia 5 by CDC2 affects its cellular distribution and is required for mitotic entry. J Biol Chem. 285(27):20904-20914.
- Chen MJ, Peng ZF, Manikandan J, Melendez AJ, Tan GS, Chung MC, Tan TM, Russo-Marie F, **Deng LW**, Moore PK & Cheung NS. (2010) Gene profiling reveal hydrogen sulphide recruits death signaling via the N-methyl-D-aspartate receptor identifying commonalities with excitotoxicity. J Cell Physiol. Oct 13. [Epub ahead of print]
- Yong QC, Cheong JL, Hua F, **Deng LW**, Khoo YM, Lee HS, Perry A, Wood M, Whiteman M & Bian JS. (2011) Regulation of heart function by endogenous gaseous mediators -Cross-talk between nitric oxide and hydrogen sulfide. Antioxid Redox Signal. Jan 2 [Epub ahead of print]
- Cheng F, Liu J, Teh C, Chong SW, Korzh V, Jiang YJ & **Deng LW** (2011) Camptothecin-induced down-regulation of MLL5 contributes to the activation of tumor suppressor p53. Accepted in Oncogene.
- Mahalingam D, Luo Z, Tan WH, Huang X, Lim YP, **Deng LW**, Cacheux-Rataboul V, Liu TB, Blackburn E & Wang X. (2011) The extra-telomeric effects of hTERT in cell migration and DNA damage initiation in neoplastic transformation of IMR90 cells. Reviewed in BMC Cancer
- Yew CW, Lee P, Chan, WK, Lim KJ, Tan MC & **Deng LW** (2011) A novel Mixed Leukemia Lineage 5 isoform is required for the activation of human papillomavirous E6 and E7 transcription in HPV16/18-postive cervical cancer cell lines (Submitted to EMBO J)
- Lee ZW, Tan CH, Chen CS, Li L, Moore PK, **Deng LW** (2011) The slow-releasing hydrogen sulfide donor, GYY4137, exhibits novel anti-cancer effects in vitro and in vivo. (Submitted to Cancer Research)

- Liu J, Huey F & **Deng LW**. (2011) Roles of MLL5 in cytokinesis and genomic instability. In preparation for Current Biology.
- Wang XN, Cheng F, Shan W, Motomi O, Jiang YJ & **Deng LW**. zMLL5 is required for myogenesis. In preparation for Dev Dynam

Invited Oral Presentation

- **Deng LW**, "Mixed Lineage Leukemia 5 in the regulation of mitotic progression and genomic integrity". *Research Seminar in Faculty of Medical and Health Sciences* (2010). Auckland: Department of Obstetrics and Gynaecology, University of Auckland. (Obstetrics and Gynaecology Special Research Seminar, 26 May 2010, Auckland City Hospital, Park Rd, Grafton, Acukland, New Zealand)
- **Deng LW**, "Mixed Lineage Leukemia 5 in the regulation of mitotic progression and genomic integrity". *UC Davis Cancer Center-Cencer Biology Research Seminar* (2010). Sacramento: UC Davis Cancer Cener. (Cancer Biology Research Seminar, 29 Apr 2010, UV Davis Cancer Center, Sacramento, United States)
- **Deng LW**. Mixed Lineage Leukemia 5 (MLL5) in Mitotic Regulation (2008). *Conférences Jacques Monod: Biological responses to DNA damage*, Center National De La Recherche Scientifique, CNRS Oct 11 – 15, Roscoff, France
- **Deng LW**, MLL5 protein forms intranuclear foci and overexpression inhibits cell cycle progression (2005). *11th East Asia Biomedical Research Symposium* Dec 12 – 15, Taipei, Taiwan.

Research Grants

- Regulation of MLL5 protein in response to DNA damage
  NUS (start-up) 01.01.2004 to 31.03.2005 $50,000
- Investigation of the associations of MLL5 with BRG1 on cell cycle regulation and transcriptional activation
  ARF 10.12.2005 to 31.12.2008 $150,000
- Elucidation of the roles of a novel protein MLL5 in cell cycle regulation and tumor suppression
  BMRC 01.02.2006 to 30.06.2009 $307,400
- Investigation of the molecular mechanism of MLL5 in response to UV irradiation
  MOE 01.06.2007 to 30.05.2010 $497,080
- Roles of mll5 in zebrafish hematopoiesis
  NMRC-EDG 01.03.2007 to 28.02.2011 $194,000
- Molecular basis of age-associated deficiency in cystathione-gamma-lyase in human lens epithelial cells: relevance in senile cataractogenesis
  NUS 01.09.2010 to 31.08.2012 $20,000
- Function of Mixed Lineage Leukemia 5 in Mitotic Spindle Integrity and Genomic Stability
  ARF 01.04.2011 to 31.03.2014 $158,950

TEACHING

Modules

- LSM1101 - Biochemistry of Biomolecules (conducted every Sem, student intake > 250)
- LSM2201 - Experimental Biochemistry Practical (conducted in Sem I)
- MD1140 - Introduction to Health & Disease (conducted in Sem I, student intake > 250)
- MD5214 - Research Skills (conducted in Sem I)
- LSM3231 - Protein Structure and Function

Research students supervised:

Undergraduate students (UROPS-Year 3; Honors-Year 4 students):

Chee Weijie Kenny	UROPS	AY2004/2005
Cheng Fei	UROPS	AY2004/2005
Huang Shu Fen (co-sup)	UROPS	AY2005/2006
Cheng Fei	Honors	AY2005/2006
I Fon Bambang	Honors	AY2005/2006
Huang Shu Fen (co-sup)	Honors	AY2006/2007
Chan Wai Keong	UROPS	AY2006/2007
Tang Qian Qiao	UROPS	AY2006/2007
Zhou Shun Hui	Honors	AY2006/2007
Chew Junfang	Honors	AY2006/2007
Chan Wai Keong	Honors	AY2007/2008
Lee Pei	Honors	AY2007/2008
Lee Huoy Fen	Honors	AY2008/2009
Ho Caifeng Jolene	Honors	AY2008/2009
Lee Zheng Wei	Honors	AY2009/2010
Low Yi Lian	Honors	AY2009/2010

Postgraduate Students:

Chen Minghui (co-sup) MSc AY2006/2009
-Thesis title: Mechanism of hydrogen sulphidemediated signaling cascade through N-methyl-D-aspartate receptors

Huang Shu Fen (co-sup) MSc AY2007/2009
-Thesis Title: Functional and Inhibitory Studies on CSE

Cheng Fei PhD AY2007- present
-Thesis to be submitted in June 2011

Liu Jie PhD AY2007- present
-Thesis to be submitted in Dec 2011

Lee Pei	MSc	AY2008- present
Yew Chow Wenn	MSc	AY2008- present