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个人简历

科研领域描述

本实验室主要兴趣在于：

1 以斑马鱼为模式研究脊椎动物早期胚胎发育基因表达调控与器官形成机制，特别是血液与心血管系统以及胰腺等内脏器官的细胞分化与发育。

2 斑马鱼功能基因组研究。

斑马鱼（Danio rerio）是进行发育生物学研究的理想模式脊椎动物。本实验室以功能基因组研究手段为切入点，通过筛选斑马鱼中与血液、心血管或胰腺发育相关的突变体与基因，鉴定基因的表达图谱，并进行基因功能以及表达调控机制的研究。

（1）新基因的筛选：应用以Tol2转座子为基础的“增强子诱捕”（enhancer-trap）技术、以绿色荧光蛋白（GFP）或红色荧光蛋白（RFP）为报告基因大规模筛选具有组织特异性表达图式的转基因斑马鱼，以及斑马鱼早期胚胎发育相关基因，以建立相应的转基因鱼系与斑马鱼基因表达模式信息库。迄今已获得1，670种报告基因带有特异表达模式的子代鱼系（F1），其中包括30种在胰腺中特异表达报告基因和40 多种在血液和/或心血管系统特异表达报告基因的鱼系；鉴定了其中的118个Tol2插入位点，附近的基因大部分为尚未见报道的新基因。这部分工作由我室与美国加州大学洛杉矶分校（UCLA）林硕教授的实验室共同合作进行。

（2）突变体的筛选：在与美国国立卫生研究院（NIH）下属的国立人类基因组研究所（NHGRI）Shawn Burgess教授进行科研合作的基础上，在国内建立了斑马鱼基因插入诱变技术平台；应用反转录病毒插入诱变技术对斑马鱼进行大规模基因饱和突变筛选，以建立斑马鱼全基因组随机突变文库与突变体信息库。这部分工作采用了高通量的LM-PCR技术，辅以大规模测序与精子冻存保种的全新策略。目前已筛选到了244个基因内的插入，其中大部分为功能未知的新基因。

最近，本实验室建立了一种构建TALE核酸酶（TAELN）的新方法，称为“Unit Assembly”，并应用TALENs在斑马鱼中成功地实现了可稳定遗传的基因组定点突变。目前，我们已经成功地突变了7个斑马鱼内源基因，其中大部分基因（5/7）的突变效率大于30%，有3个基因的突变效率甚至接近100%。

胰腺是一个既包含内分泌腺又包含外分泌腺的特殊的复合器官，它的形态发生既涉及到多种信号通路参与的复杂的细胞分化过程，又存在细胞大量扩增的发育阶段，是研究体内细胞增殖与分化的良好模式。同时，糖尿病、胰腺癌等严重危害人类健康的疾病与胰腺的发育缺陷与功能失调密切相关，因而胰腺发育机制的研究具有不言而喻的理论与应用价值。然而，胰腺作为一个内脏器官，由于其深陷在身体内部而难以进行深入研究，因此胰腺的发育机制研究相对其它器官而言比较滞后。在上述通过Tol2增强子诱捕筛选得到的胰腺被特异标记的鱼系中，GFP报告基因的可视标记无疑为我们研究胰腺提供了一个极好的条件。我们将充分发挥上述转基因鱼系与突变体的优势，以胰腺的发育为模式，研究细胞增殖与分化在胰腺形成中的作用及其机制。

人类对脊椎动物造血系统以及心血管系统的研究已有几百年的历史，但是它们的发育机制尚未完全阐明。脊椎动物进化过程中造血过程与心血管的发生是高度保守的，并且造血系统和血管系统共同起源于腹侧中胚层（ventral mesoderm），两者可能具有共同的前体细胞—成血成血管干细胞（hemangioblast），经进一步诱导分化形成成血细胞（hematopoietic stem cell）及成血管细胞（angioblast）。丰富的细胞类型与逐级的分化过程使造血系统成为研究体内细胞增殖与分化调控机制的理想体系。斑马鱼胚胎在受精后24小时即可开始心脏跳动与血液循环，并且胚胎通体透明，血红素呈红色，在体视镜下极易观察；更为宝贵的是，循环系统有缺陷的斑马鱼胚胎依然能够依靠体表的气体交换存活几天，这样就为我们研究发生缺陷的原因争取了时间。无疑，斑马鱼是开展血液与心血管发育机制研究的理想材料。我们将从上述Tol2增强子诱捕与反转录病毒插入诱变的筛选结果中，选择血液和/或心血

管系统特异的基因与突变体，深入研究细胞增殖与分化在脊椎动物血液与心血管系统发育过程中的作用及其调控机制。

Research Description:

Zebrafish (Danio rerio) is an excellent model animal to study vertebrate development by genetic approaches. Using zebrafish as a major animal model, we are interested in: (1) Genetic and developmental mechanisms of vertebrate embryogenesis and organogenesis, especially those related to hematopoiesis, cardiovascular development and pancreas formation. (2) Functional genomics study.

As an entry point, we have recently conducted the following two genome-wide, large scale genetic screening for genes either with tissue-specific expression patterns or with mutations.

a. Using GFP or RFP as the reporter gene, we have performed a Tol2 transposon-mediated large-scale enhancer trap screen in zebrafish. A total of 1, 670 individual F1 transgenic fish lines were isolated, including 30 pancreas and more than 40 hematopoietic and/or cardiovascular specific transgenic lines. Totally 118 insertion sites have been identified, most of which are flanked by novel genes. This project is in collaboration with Prof. Shuo Lin from UCLA of USA.

b. We have established a zebrafish mutagenesis platform based on retrovirus mediated insertion, and are aiming at generating a mutant library via random insertion of the pseudo-typed retrovirus. So far we have obtained 244 insertions that reside in genes, most of which are functionally unknown. This project is in collaboration with Prof. Shawn Burgess from NHGRI at NIH of USA.

Recently, we have developed a new method called “Unit Assembly” to assemble TALE nuclease (TALEN) and achieved heritable gene targeting in zebrafish by using TALEN technique. So far seven genes have been successfully targeted via TALENs in our lab, where more half of the TALEN pairs showed more than 50% targeting activity, with three pairs of them led to nearly 100% target site disruption after injection of mRNA pairs into one-cell stage zebrafish embryos.

The pancreas contains endocrine and exocrine compartments that both exert important physiological functions. The development of pancreas is a dynamic process of cell proliferation and differentiation which are controlled at molecular levels involving extrinsic signals from the surrounding tissues and intrinsic transcriptional programs. Pancreas cancer has been one of the most poorly understood diseases. Majority of pancreatic cancers originate from uncontrolled expansion of exocrine pancreas. Understanding the mechanisms of cell proliferation during normal pancreas development is important for the comprehending of pancreatic carcinogenesis. It is known that both endocrine cells and exocrine cells derive from the same population of progenitor cells. However, how the progenitor cells adopt different cell fate in response to extrinsic signals as well as how these cells undergo rapid lineage specific proliferation during embryogenesis is not fully understood. We have obtained 30 pancreas specific transgenic lines from our previous Tol2 enhancer trap screen, which gives us a unique opportunity to address these questions in zebrafish.

Hematopoiesis and blood vessel formation are highly conserved among vertebrates. It has been shown that blood cells and blood vessel cells, which are both derived from ventral mesoderm, share common ancestors called hemangioblasts. These hemangioblasts will give rise to hematopoietic stem cells and angioblasts, which, through complicated cell proliferation and differentiation processes, will further differentiate into various types of mature blood cells and blood vessels, respectively. Zebrafish is an ideal model for the analysis of hematopoiesis and cardiovascular development due to its rapid external embryonic development and transparency. These processes can be visualized in live embryos using transgenic fluorescent protein reporters and embryos can survive for several days without circulating blood cells. We aim to study how cell proliferation and differentiation are involved in hematopoiesis and cardiovascular development based on the hematopoietic and/or cardiovascular specific transgenic and mutant zebrafish obtained from the above-mentioned screens.

代表性论文

1. Zu, Y., Tong, X., Wang, Z., Liu, D., Pan, R., Li, Z., Hu, Y., Luo, Z., Huang, P., Wu, Q., Zhu, Z., Zhang, B., Lin, S. , TALEN-mediated precise genome modification by homologous recombination in zebrafish. , Nat. Methods , 2013 , 10 (4): 329-331. (Cover story)

2. Wei, C., Liu, J., Yu, Z., Zhang, B., Gao, G. and Jiao, R. , TALEN or Cas9 -- rapid, efficient and specific choices for genomic modifications. , J. Genet. Genomics , 2013 , DOI: 10.1016/j.jgg.2013.03.013. (Invited review)

3. Xiao, A., Wang, Z., Hu, Y., Wu, Y., Luo, Z., Yang, Z., Zu, Y., Li, W., Huang, P., Tong, X., Zhu, Z., Lin, S. and Zhang, B. , Chromosomal deletions and inversions mediated by TALENs and

CRISPR/Cas in zebrafish. , Nucleic Acids Res. , 2013 , (In press)
4. Huang, P., Zhu, Z., Lin, S. and Zhang, B. , Reverse genetic approaches in zebrafish , J. Genet. Genomics , 2012 , 39 (9): 421-433. (Invited review)
5. Huang, P., Xu, L., Liang, W., Tam, C. I., Zhang, Y., Qi, F., Zhu, Z., Lin, S. and Zhang, B. , Genomic deletion induced by Tol2 transposon excision in zebrafish. , Nucleic Acids Res. , 2012 , 41 (2): e36.
6. Tong, X., Xia, Z., Zu, Y., Telfer H., Hu, J., Yu, J., Liu, H., Zhang, Q., Sodmergen, Lin, S. and Zhang, B. , Ngs (notochord granular surface) encodes a novel type of intermediate filament family protein essential for notochord maintenance in zebrafish. , J. Biol. Chem. , 2012 , 288 (4): 2711-2720.
7. Xiao, A., Wu, Y., Yang, Z., Hu, Y., Wang, W., Zhang, Y., Kong, L., Gao, G., Zhu, Z., Lin, S. and Zhang, B. , EENdb: a database and knowledge base of ZFNs and TALENs for endonuclease engineering. , Nucleic Acids Res. , 2012 , 41: D415-D422.
8. Gao, W., Xu, L., Guan, R., Liu, X., Han, Y., Wu, Q., Xiao, Y., Qi, F., Zhu, Z., Lin, S. and Zhang, B. , Wdr18 is required for Kupffer's vesicle formation and regulation of body asymmetry in zebrafish. , PLoS ONE , 2011 , 6 (8): e23386. , [Abstract] , [Full Text]
9. Huang, P., Xiao, A., Zhou, M., Zhu, Z., Lin, S. and Zhang, B. , Heritable gene targeting in zebrafish using customized TALENs. , Nat. Biotechnol. , 2011 , 29 (8): 699-700. , [Abstract] , [Full Text]
10. Jiang, Z., Song, J., Qi, F., Xiao, A., An, X., Liu, N. A., Zhu, Z., Zhang, B. and Lin S. , Exdpf is a key regulator of exocrine pancreas development controlled by retinoic acid and ptf1a in zebrafish. , PLoS Biol. , 2008 , 6 (11): e293. , [Abstract] , [Full Text]
11. Wei, W., Wen, L., Huang, P., Zhang, Z., Chen, Y., Xiao, A., Huang, H., Zhu, Z., Zhang, B. and Lin, S , Gfi1.1 regulates hematopoietic lineage differentiation during zebrafish embryogenesis , Cell Res. , 2008 , 18: 677-685. , [Abstract] , [Full Text]
12. Wen, L., Wei, W., Gu, W., Huang, P., Ren, X., Zhang, Z., Zhu, Z., Lin, S. and Zhang, B., , Visualization of monoaminergic neurons and neurotoxicity of MPTP in live transgenic zebrafish , Dev. Biol. , 2008 , 314 (1): 84-92. , [Abstract] , [Full Text]
13. Wang, D., Jao, L.-E., Zheng, N., Dolan, K., Ivey, J., Zonies, S., Wu, X., Wu, K., Yang, H., Meng, Q., Zhu, Z., Zhang, B., Lin, S. and Burgess, S. M , Efficient genome-wide mutagenesis of zebrafish genes by retroviral insertions , Proc. Natl. Acad. Sci. USA , 2007 , 104 (30): 12428-12433. , [Abstract] , [Full Text]
14. Liu, B., Lee, K. W., Anzo, M., Zhang, B., Zi, X., Tao, Y., Shiry, L., Pollak, M., Lin, S. and Cohen, P , Insulin-like growth factor-binding protein-3 inhibition of prostate cancer growth involves suppression of angiogenesis , Oncogene , 2006 , 26(12): 1811-1819
15. Zhang J. Z., Gao W., Yang H. B., Zhang B., Zhu Z. Y. and Xue Y. F , Screening for genes essential for mouse embryonic stem cell self-renewal using a subtractive RNA interference library , Stem Cells , 2006 , 24(12): 2661-2668
16. Huang, H., Zhang, B., Hartenstein, P. A., Chen, J. N. and Lin, S , NXT2 is required for embryonic heart development in zebrafish , BMC Dev. Biol., , 2005 , 5(1): 7
17. Sumanas S., Zhang B., Dai R., Lin S , 15-zinc finger protein Bloody Fingers is required for zebrafish morphogenetic movements during neurulation , Dev Biol., , 2005 , 283(1): 85-96
18. Zhang B., Georgiev O., Hagmann M., Günes ?., Faller P., Va?ák M. and Schaffner W , Activation of metal transcription factor-1 (MTF-1) by toxic heavy metals and H2O2 in vitro is modulated by metallothionein , Mol. Cell. Biol., , 2003 , 23(23): 8471-8485
19. Zhang B., Egli D., Georgiev O. and Schaffner W , The Drosophila homolog of mammalian zinc finger factor MTF-1 activates transcription in response to heavy metals , Mol. Cell. Biol., , 2001 , 21(14): 4505-4514