学校编码：10384

学号：20120051403141

厦门大学

博 士 学 位 论 文

核孤儿受体TR3 的磷酸化和异构化修饰以及对Wnt信号通路的调控

Phosphorylation and isomerization of nuclear orphan receptor TR3 and its regulation on Wnt signaling pathway

陈航姿

指导教师：吴乔

专业名称：细胞生物学

答辩日期：2009年5月

厦门大学学位论文原创性声明

本人呈交的学位论文是本人在导师指导下，独立完成的研究成果。本人在论文写作中参考其他个人或集体已经发表的研究成果，均在文中以适当方式明确标明，并符合法律规范和《厦门大学研究生学术活动规范（试行）》。

另外，该学位论文为（　　）课题（组）的研究成果，获得（　　）课题（组）经费或实验室的资助，在（　　）实验室完成。（请在以上括号内填写课题或课题组负责人或实验室名称，未有此项声明内容的，可以不作特别声明。）

声明人（签名）：

年　月　日

厦门大学学位论文著作权使用声明

本人同意厦门大学根据《中华人民共和国学位条例暂行实施办法》等规定保留和使用此学位论文，并向主管部门或其指定机构送交学位论文(包括纸质版和电子版)，允许学位论文进入厦门大学图书馆及其数据库被查阅、借阅。本人同意厦门大学将学位论文加入全国博士、硕士学位论文共建单位数据库进行检索，将学位论文的标题和摘要汇编出版，采用影印、缩印或者其它方式合理复制学位论文。

本学位论文属于:

(　　)1.经厦门大学保密委员会审查核定的保密学位论文，于　年　月　日解密，解密后适用上述授权。

(　　)2.不保密，适用上述授权。

(请在以上相应括号内打“✓”或填上相应内容。保密学位论文应是已经厦门大学保密委员会审定过的学位论文，未经厦门大学保密委员会审定的学位论文均为公开学位论文。此声明栏不填写的，默认为公开学位论文，均适用上述授权。)

声明人(签名):

年　　月　　日

摘 要

摘　　要

第一章　核孤儿受体TR3概述

TR3（又被称为NGFI-B、Nur77）是一种核受体，属于类固醇/甲状腺/视黄酸受体家族成员。由于目前尚未发现TR3特异性配体，因此被称为核孤儿受体。TR3是一种立早基因，可以被许多生长因子或凋亡因子迅速诱导表达，其转录后水平的修饰则影响着TR3功能的发挥。作为转录因子，TR3通过与其应答元件NBRE或NurRE的结合，调控着许多基因的转录，从而参与对细胞增殖、凋亡、新陈代谢以及炎症反应等方面的调控。另一方面，TR3的亚细胞定位也影响着生物学功能的发挥。当TR3从细胞核转运到细胞浆并定位于线粒体后，将使Bcl-2由凋亡抑制蛋白转变为凋亡诱导蛋白，并最终诱导细胞凋亡。此外，TR3还可以作为调控蛋白，通过与其他蛋白的相互作用来影响它们生物学功能的发挥。总之，TR3在体内经过复杂的调控网络，以不同的作用方式发挥着各种各样的生物学功能。

第二章　Akt磷酸化TR3抑制其线粒体定位

Akt通过对底物蛋白的磷酸化修饰影响底物的功能，并因此调控细胞的新陈代谢、凋亡、增殖等。但是，Akt究竟如何促进细胞存活，抑制细胞凋亡的机理尚未被详尽地阐明。TR3通过对其下游基因表达的调控，参与了对细胞增殖和细胞凋亡的调控。我们实验室早期的研究已经证明，在胃癌细胞中， TR3可以通过由细胞核转运到细胞浆并定位于线粒体而促进细胞凋亡。在本章节研究中我们发现，Akt通过与TR3 N端的结合可以磷酸化其N端。在胃癌细胞BGC823中过表达Akt显著

地抑制TR3的线粒体定位和由此引发的肿瘤细胞凋亡，而显性负作用的Akt突变体则丧失这种能力。进一步研究表明，Akt对TR3 N端的磷酸化阻断了TR3与Bcl-2的结合，而该结合是TR3定位于线粒体先决条件。用Akt的激活剂胰岛素处理细胞则以PI3K活性依赖的方式显著削弱了TPA诱导的细胞凋亡。因此，本文的研究阐明了一种Akt抑制细胞凋亡的新途径：Akt通过对核受体TR3的磷酸化修饰，调控TR3的核浆定位，从而阻断TR3诱导的肿瘤细胞凋亡。

第三章 Pin1异构化TR3在细胞生长和凋亡的双重功能

Pin1是一种蛋白脯氨酰顺反式异构酶，通过对磷酸化底物上的pSer/Thr-Pro异构化修饰，参与了细胞信号转导过程中的各种调控。TR3在不同形式的转录后修饰下，既能促进细胞增殖，又能诱导细胞凋亡。在本章节研究中我们发现，TR3是Pin1的新底物。TR3分子上至少有3个位点可以与Pin1结合，分别是Ser95-Pro、Ser140-Pro和Ser431-Pro。Pin1与三个不同位点的结合可以调控TR3不同的功能：与Ser95-Pro的结合提高了TR3的蛋白稳定性，与Ser431-Pro的结合则提高了TR3的转录激活活性并影响TR3的核浆定位。我们还发现，cyclin D2作为一个TR3新的下游基因，其表达水平直接受TR3的调控。Pin1通过对TR3的调控表现出双重功能。一方面，在生长因子刺激下，Pin1通过促进TR3与cyclin D2启动子的结合，增强了TR3募集转录辅激活因子p300的能力，从而提高cyclin D2的表达，促进细胞增殖；而另一方面，在凋亡诱导剂TPA的刺激下，Pin1增强了TR3的出核转运和线粒体定位，从而促进TR3介导的细胞凋亡。裸鼠移植瘤实验进一步证实了Pin1可以通过TR3影响移植瘤的生长。因此，本文的研究阐明了Pin1通过对TR3的异构化修饰，调控细胞增殖和细胞凋亡两个截然不同的生物学功能。

第四章　TR3负调控Wnt信号通路的分子机理

Wnt信号通路是机体中至关重要的信号转导通路，它直接影响着机体的发育、生长以及肿瘤发生等过程。当Wnt配体与细胞表面受体结合后，通过一系列的蛋白相互调控，抑制β-Catenin的磷酸化和泛素化降解，使β-Catenin由细胞浆转运到细胞核，并与TCF/LEF结合，从而激活Wnt信号。我们实验室的前期研究已经发现，TR3可以作为转录阻遏蛋白通过抑制转录辅激活因子的活性来抑制相关基因的转录。在本章节中，我们发现TR3可以显著地抑制Wnt信号活性，无论是生理上的由Wnt配体激活的Wnt信号活性、还是病理上的由无法被降解的β-Catenin突变体激活的Wnt信号活性、或者是结肠癌细胞中持续激活的Wnt信号活性均可以被TR3抑制。虽然TR3既不影响细胞中β-Catenin的mRNA和蛋白的表达水平，也不影响β-Catenin的核浆定位，但TR3与β-Catenin的结合却阻断了β-Catenin与DNA的结合，由此抑制Wnt下游基因c-myc和cyclin D1的蛋白表达。Wnt信号的负调控因子Axin和GSK则通过提高TR3蛋白的稳定性进一步加强TR3对Wnt信号的抑制作用。此外，在裸鼠移植瘤实验中，TR3的特异性激动剂Csn-B以TR3依赖的方式抑制结肠癌细胞SW620移植瘤的生长。因此，本文的研究阐明了一条TR3通过抑制Wnt信号来抑制肿瘤生长的信号调控新途径。

关键词：TR3; Akt; Pin1; Wnt 信号通路

Abstract

Abstract

Chapter 1 Overview of orphan receptor TR3

The immediate-early gene product TR3 (also known as Nur77 or NGFI-B) is a nuclear receptor of the steroid/thyroid/retinoid receptor superfamily. Since its physiological ligand has not been identified, TR3 is also termed as orphan receptor. The expression of TR3 can be immediately induced by many growth factors and pro-apoptotic factors. As a transcriptional factor, TR3 regulates the transcription of many genes through binding to its response element, therefore playing important roles in cell proliferation, apoptosis, metabolism and inflammatory reaction. In addition, the subcellular localization of TR3 is also important for its biological functions. When translocation from the nucleus to the mitochondria, TR3 interacts with Bcl-2 and converts Bcl-2 from a cytoprotective to a cytodestructive protein to trigger apoptosis. Moreover, TR3 can also regulate the function of other proteins through protein-protein interaction. Therefore, in this chapter, we provide an overview of TR3, and demonstrate that after complicated modifications, TR3 can exert different biological functions through diverse regulation fashions.

Chapter 2. Akt phosphorylates TR3 and blocks its mitochondrial targeting

Akt phosphorylates and regulates the function of many cellular proteins involved

in processes such as metabolism, apoptosis, and proliferation. However, the precise mechanisms by which Akt promotes cell survival and inhibits apoptosis have been characterized in part only. TR3, an orphan receptor, functions as a transcription factor that can both positively or negatively regulate gene expression. We have previously reported that the translocation of TR3 from the nucleus to the mitochondria can elicit a proapoptotic effect in gastric cancer cells. In our present study, we demonstrate that Akt phosphorylates cytoplasmic TR3 through its physical interaction with the N-terminus of TR3. When co-expressed with Akt, TR3 mitochondrial targeting was blocked and this protein adopted a diffuse expression pattern in the cytoplasm. Moreover, Akt displayed an ability to disrupt the interaction of TR3 with Bcl-2, which is thought to be a critical requirement for mitochondrial TR3 to elicit apoptosis. Consistently, insulin was also found to induce the phosphorylation of TR3 and abolish TPA-induced mitochondrial localization, which was dependent upon the activation of the PI3K-Akt signaling pathway. Taken together, our current data demonstrate a unique role for Akt in inhibiting TR3 functions that are not related to transcriptional activity but that correlate with the regulation of its mitochondrial association. This may represent a novel signal pathway by which Akt exerts its anti-apoptotic effects in gastric cancer cells, i.e. by regulating the phosphorylation and redistribution of orphan receptors.

Chapter 3. Isomerization of TR3 by Pin1 plays a dual role in cell proliferation and apoptosis

Pin1 regulates a subset of phosphoproteins by isomerizing Ser/Thr-Pro motifs via

post-phosphorylation mechanisms. In our current study, we characterize TR3 as a novel Pin1 substrate. We show that (1) phosphorylation of TR3 by ERK facilitates the recognition and binding of Pin1; (2) TR3 Ser95 residue is the key site through which Pin1 enhances TR3 stability by inhibiting its degradation; and (3) the isomerization of Ser431-Pro motif in TR3 by Pin1 results in the activation of TR3 by enhancing its DNA binding affinity. Furthermore, we find that Pin1 not only enhances TR3 targeting to the promoter of cyclin D2, which is a novel downstream of TR3, but also promotes the TR3 recruitment of p300, ultimately resulting in increased cell proliferation. On the other hand, Pin1 is found also to assist TR3 nuclear export and mitochondrial targeting in response to TPA, thereby initiating cellular apoptosis. The regulatory role of Pin1 in the TR3 pathways is further confirmed by an in vivo tumor formation assay. Our current study thus demonstrates that Pin1 plays a dual role in cell proliferation and apoptosis by isomerizing TR3.

Chapter 4. Molecular mechanism of TR3 in negative regulation of Wnt signaling pathway

Wnt signaling controls various cell fates, including development, proliferation and tumorigenesis. Binding of Wnt ligand to its transmembrane receptors inhibits phosphorylation and degradation of the transcriptional coactivator β-Catenin, which then results in the translocation of β-Catenin from the cytoplasm to the nucleus to regulate the expression of target genes. Our previous study has indicated that TR3 serves as a transcriptional repressor to inhibit the activities of many co-activators. In the current study, we showed that TR3 modulates Wnt

signaling, either physiologically by Wnt ligands or pathologically by APC inactivation or β-catenin activation. Although TR3 does not show any influences on the expression levels of β-Catenin, the interaction between TR3 and β-Catenin disrupts the β-Catenin DNA binding, thereby inhibiting the expression of Wnt downstream proteins, such as c-myc and cyclin D1. In addition, Axin and GSK3β, negative regulators of Wnt signaling, cooperate with TR3 to repress the activity of Wnt signal. Moreover, in nude mice xenograft experiment, we also confirmed that Csn-B, a specific TR3 agonist, represses tumor growth in a TR3-dependent fashion. Taken together, our study demonstrates a novel function of TR3 as a tumor suppressor to inhibit the Wnt signaling pathway.

Keywords: TR3; Akt; Pin1; Wnt signaling

参考资料

参 考 文 献

第一章

1. Hollenberg, S. M. et al. Primary structure and expression of a functional human glucocorticoid receptor cDNA [J]. Nature 1985. 318, 635-641

2. A unified nomenclature system for the nuclear receptor superfamily [J]. Cell 1999. 97, 161-163

3. Germain, P., Staels, B., Dacquet, C., Spedding, M. & Laudet, V. Overview of nomenclature of nuclear receptors [J]. Pharmacol. Rev. 2006. 58, 685-704

4. Hazel, T. G., Nathans, D. & Lau, L. F. A gene inducible by serum growth factors encodes a member of the steroid and thyroid hormone receptor superfamily [J]. Proc. Natl. Acad. Sci. U. S. A 1988. 85, 8444-8448

5. Hedvat, C. V. & Irving, S. G. The isolation and characterization of MINOR, a novel mitogen-inducible nuclear orphan receptor [J]. Mol. Endocrinol. 1995. 9, 1692-1700

6. Li, H. et al. Cytochrome c release and apoptosis induced by mitochondrial targeting of nuclear orphan receptor TR3 [J]. Science 2000. 289, 1159-1164

7. Lau, L. F. & Nathans, D. Identification of a set of genes expressed during the G0/G1 transition of cultured mouse cells [J]. EMBO J. 1985. 4, 3145-3151

8. Milbrandt, J. Nerve growth factor induces a gene homologous to the glucocorticoid receptor gene [J]. Neuron 1988. 1, 183-188

9. Watson, M. A. & Milbrandt, J. The NGFI-B gene, a transcriptionally inducible member of the steroid receptor gene superfamily: genomic structure and expression in rat brain after seizure induction [J]. Mol. Cell Biol. 1989. 9, 4213-4219

10. Chang, C., Kokontis, J., Liao, S. S. & Chang, Y. Isolation and characterization of human TR3 receptor: a member of steroid receptor superfamily [J]. J. Steroid Biochem. 1989. 34, 391-395

11. Ohkura, N., Hijikuro, M., Yamamoto, A. & Miki, K. Molecular cloning of a novel thyroid/steroid receptor superfamily gene from cultured rat neuronal cells [J]. Biochem. Biophys. Res. Commun. 1994. 205, 1959-1965

12. Law, S. W., Conneely, O. M., DeMayo, F. J. & O'Malley, B. W. Identification of a new brain-specific transcription factor, NURR1 [J]. Mol. Endocrinol. 1992. 6, 2129-2135

13. Martinez-Gonzalez, J. & Badimon, L. The NR4A subfamily of nuclear receptors: new early genes regulated by growth factors in vascular cells [J]. Cardiovasc. Res. 2005. 65, 609-618

14. Davis, I. J., Hazel, T. G., Chen, R. H., Blenis, J. & Lau, L. F. Functional domains and phosphorylation of the orphan receptor Nur77 [J]. Mol. Endocrinol. 1993. 7, 953-964

15. Maira, M., Martens, C., Batsche, E., Gauthier, Y. & Drouin, J. Dimer-specific potentiation of NGFI-B (Nur77) transcriptional activity by the protein kinase A pathway and AF-1-dependent coactivator recruitment [J]. Mol. Cell Biol. 2003. 23, 763-776

16. Wansa, K. D., Harris, J. M. & Muscat, G. E. The activation function-1 domain of Nur77/NR4A1 mediates trans-activation, cell specificity, and coactivator recruitment [J]. J. Biol. Chem. 2002. 277, 33001-33011

17. Woronicz, J. D., Calnan, B., Ngo, V. & Winoto, A. Requirement for the orphan steroid receptor Nur77 in apoptosis of T-cell hybridomas [J]. Nature 1994. 367, 277-281

18. Meinke, G. & Sigler, P. B. DNA-binding mechanism of the monomeric orphan nuclear receptor NGFI-B [J]. Nat. Struct. Biol. 1999. 6, 471-477

19. Giguere, V. Orphan nuclear receptors: from gene to function [J]. Endocr. Rev. 1999. 20, 689-725

20. Katagiri, Y. et al. Modulation of retinoid signalling through NGF-induced nuclear export of NGFI-B [J]. Nat. Cell Biol. 2000. 2, 435-440

21. Lin, B. et al. Conversion of Bcl-2 from protector to killer by interaction with nuclear orphan receptor Nur77/TR3 [J]. Cell 2004. 116, 527-540

22. Wang, Z. et al. Structure and function of Nurr1 identifies a class of ligand-independent nuclear receptors [J]. Nature 2003. 423, 555-560
23. Baker, K. D. et al. The Drosophila orphan nuclear receptor DHR38 mediates an atypical ecdysteroid signaling pathway [J]. Cell 2003. 113, 731-742
24. Flaig, R., Greschik, H., Peluso-Iltis, C. & Moras, D. Structural basis for the cell-specific activities of the NGFI-B and the Nurr1 ligand-binding domain [J]. J. Biol. Chem. 2005. 280, 19250-19258
25. H.Eric Xu & Yong Li. Ligand-Dependent and -Independent Regulation of PPAR and Orphan Nuclear Receptors [J]. Sci. Signal. 2008. 1, pe52
26. Zhan, Y. et al. Cytosporone B is an agonist for nuclear orphan receptor Nur77 [J]. Nat. Chem. Biol. 2008. 4, 548-556
27. Bandoh, S., Tsukada, T., Maruyama, K., Ohkura, N. & Yamaguchi, K. Differential expression of NGFI-B and RNR-1 genes in various tissues and developing brain of the rat: comparative study by quantitative reverse transcription-polymerase chain reaction [J]. J. Neuroendocrinol. 1997. 9, 3-8
28. Uemura, H. & Chang, C. Antisense TR3 orphan receptor can increase prostate cancer cell viability with etoposide treatment [J]. Endocrinology 1998. 139, 2329-2334
29. Wu, Q., Liu, S., Ye, X. F., Huang, Z. W. & Su, W. J. Dual roles of Nur77 in selective regulation of apoptosis and cell cycle by TPA and ATRA in gastric cancer cells [J]. Carcinogenesis 2002. 23, 1583-1592
30. Jeong, J. H. et al. Orphan nuclear receptor Nur77 translocates to mitochondria in the early phase of apoptosis induced by synthetic chenodeoxycholic acid derivatives in human stomach cancer cell line SNU-1 [J]. Ann. N. Y. Acad. Sci. 2003. 1010, 171-177
31. Wu, W. S., Xu, Z. X., Ran, R., Meng, F. & Chang, K. S. Promyelocytic leukemia protein PML inhibits Nur77-mediated transcription through specific functional interactions [J]. Oncogene 2002. 21, 3925-3933
32. Maddika, S. et al. Cancer-specific toxicity of apoptin is independent of death receptors but involves the loss of mitochondrial membrane potential and the release of mitochondrial cell-death mediators by a Nur77-dependent pathway [J]. J. Cell Sci. 2005. 118, 4485-4493
33. Lim, R. W., Varnum, B. C. & Herschman, H. R. Cloning of tetradecanoyl phorbol ester-induced 'primary response' sequences and their expression in density-arrested Swiss 3T3 cells and a TPA non-proliferative variant [J]. Oncogene 1987. 1, 263-270
34. Liu, D., Jia, H., Holmes, D. I., Stannard, A. & Zachary, I. Vascular endothelial growth factor-regulated gene expression in endothelial cells: KDR-mediated induction of Egr3 and the related nuclear receptors Nur77, Nurr1, and Nor1 [J]. Arterioscler. Thromb. Vasc. Biol. 2003. 23, 2002-2007
35. Kolluri, S. K. et al. Mitogenic effect of orphan receptor TR3 and its regulation by MEKK1 in lung cancer cells [J]. Mol. Cell Biol. 2003. 23, 8651-8667
36. Lammi, J. & Aarnisalo, P. FGF-8 stimulates the expression of NR4A orphan nuclear receptors in osteoblasts [J]. Mol. Cell Endocrinol. 2008. 295, 87-93
37. Williams, G. T. & Lau, L. F. Activation of the inducible orphan receptor gene nur77 by serum growth factors: dissociation of immediate-early and delayed-early responses [J]. Mol. Cell Biol. 1993. 13, 6124-6136
38. Liu, S. et al. Induction of apoptosis by TPA and VP-16 is through translocation of TR3 [J]. World J. Gastroenterol. 2002. 8, 446-450
39. Cao, X. et al. Retinoid X receptor regulates Nur77/TR3-dependent apoptosis [corrected] by modulating its nuclear export and mitochondrial targeting [J]. Mol. Cell Biol. 2004. 24, 9705-9725
40. Gennari, A. et al. Identification by DNA macroarray of nur77 as a gene induced by di-n-butyltin dichloride: its role in organotin-induced apoptosis [J]. Toxicol. Appl. Pharmacol. 2002. 181, 27-31
41. Shin, H. J. et al. Induction of orphan nuclear receptor Nur77 gene expression and its role in cadmium-induced apoptosis in lung [J]. Carcinogenesis 2004. 25, 1467-1475
42. Chinnaiyan, P. et al. Enhancing the antitumor activity of ErbB blockade with histone deacetylase (HDAC) inhibition [J]. Int. J. Cancer 2006. 118, 1041-1050
43. Chintharlapalli, S. et al. Activation of Nur77 by selected 1,1-Bis(3'-indolyl)-1-(p-substituted

phenyl)methanes induces apoptosis through nuclear pathways [J]. J. Biol. Chem. 2005. 280, 24903-24914
44. Yoo, Y. G. et al. 6-Mercaptopurine, an activator of Nur77, enhances transcriptional activity of HIF-1alpha resulting in new vessel formation [J]. Oncogene 2007. 26, 3823-3834
45. Chen, Y. L. et al. The induction of orphan nuclear receptor Nur77 expression by n-butylenephthalide as pharmaceuticals on hepatocellular carcinoma cell therapy [J]. Mol. Pharmacol. 2008. 74, 1046-1058
46. Lin, P. C. et al. Orphan nuclear receptor, Nurr-77 was a possible target gene of butylidenephthalide chemotherapy on glioblastoma multiform brain tumor [J]. J. Neurochem. 2008. 106, 1017-1026
47. Liu, J. et al. Modulation of orphan nuclear receptor Nur77-mediated apoptotic pathway by acetylshikonin and analogues [J]. Cancer Res. 2008. 68, 8871-8880
48. Pei, L. et al. NR4A orphan nuclear receptors are transcriptional regulators of hepatic glucose metabolism [J]. Nat. Med. 2006. 12, 1048-1055
49. Pei, L., Castrillo, A., Chen, M., Hoffmann, A. & Tontonoz, P. Induction of NR4A orphan nuclear receptor expression in macrophages in response to inflammatory stimuli [J]. J. Biol. Chem. 2005. 280, 29256-29262
50. Moldovan, S. M., Nervina, J. M., Tetradis, S. & Camargo, P. M. Regulation of Nur77 gene expression by prostanoids in cementoblastic cells [J]. Arch. Oral Biol. 2009.
51. Nogueira, E. F. et al. Angiotensin-II acute regulation of rapid response genes in human, bovine, and rat adrenocortical cells [J]. J. Mol. Endocrinol. 2007. 39, 365-374
52. Youn, H. D., Sun, L., Prywes, R. & Liu, J. O. Apoptosis of T cells mediated by Ca2+-induced release of the transcription factor MEF2 [J]. Science 1999. 286, 790-793
53. Woronicz, J. D. et al. Regulation of the Nur77 orphan steroid receptor in activation-induced apoptosis [J]. Mol. Cell Biol. 1995. 15, 6364-6376
54. Youn, H. D., Chatila, T. A. & Liu, J. O. Integration of calcineurin and MEF2 signals by the coactivator p300 during T-cell apoptosis [J]. EMBO J. 2000. 19, 4323-4331
55. Kasler, H. G., Victoria, J., Duramad, O. & Winoto, A. ERK5 is a novel type of mitogen-activated protein kinase containing a transcriptional activation domain [J]. Mol. Cell Biol. 2000. 20, 8382-8389
56. Sung Ouk Kim, Koh Ono, Peter S.Tobias & Jiahuai Han Orphan Nuclear Receptor Nur77 Is Involved in Caspase-independent Macrophage Cell Death [J]. The Journal of Experimental Medicine 2003. 197, 1441-1452
57. Liu, X., Chen, X., Zachar, V., Chang, C. & Ebbesen, P. Transcriptional activation of human TR3/nur77 gene expression by human T-lymphotropic virus type I Tax protein through two AP-1-like elements [J]. J. Gen. Virol. 1999. 80 (Pt 12), 3073-3081
58. Stocco, C. O., Lau, L. F. & Gibori, G. A calcium/calmodulin-dependent activation of ERK1/2 mediates JunD phosphorylation and induction of nur77 and 20alpha-hsd genes by prostaglandin F2alpha in ovarian cells [J]. J. Biol. Chem. 2002. 277, 3293-3302
59. Fass, D. M., Butler, J. E. & Goodman, R. H. Deacetylase activity is required for cAMP activation of a subset of CREB target genes [J]. J. Biol. Chem. 2003. 278, 43014-43019
60. Darragh, J. et al. MSKs are required for the transcription of the nuclear orphan receptors Nur77, Nurr1 and Nor1 downstream of MAPK signalling [J]. Biochem. J. 2005. 390, 749-759
61. Pei, L., Castrillo, A. & Tontonoz, P. Regulation of macrophage inflammatory gene expression by the orphan nuclear receptor Nur77 [J]. Mol. Endocrinol. 2006. 20, 786-794
62. Chao, L. C., Bensinger, S. J., Villanueva, C. J., Wroblewski, K. & Tontonoz, P. Inhibition of adipocyte differentiation by Nur77, Nurr1, and Nor1 [J]. Mol. Endocrinol. 2008. 22, 2596-2608
63. Bassam El-Asmar, , X. C. G. & Jacques J Tremblay. Transcriptional cooperation between NF-B p50 and CCAAT/enhancer binding protein beta regulates Nur77 transcription in Leydig cells. 42, 131-138. 2009.
Ref Type: Generic
64. Lacroix, M., Toillon, R. A. & Leclercq, G. p53 and breast cancer, an update [J]. Endocr. Relat Cancer 2006. 13, 293-325
65. Winoto, A. & Littman, D. R. Nuclear hormone receptors in T lymphocytes [J]. Cell 2002. 109 Suppl, S57-S66

66. Fahrner, T. J., Carroll, S. L. & Milbrandt, J. The NGFI-B protein, an inducible member of the thyroid/steroid receptor family, is rapidly modified posttranslationally [J]. Mol. Cell Biol. 1990. 10, 6454-6459
67. Han, Y. H. et al. Regulation of Nur77 nuclear export by c-Jun N-terminal kinase and Akt [J]. Oncogene 2006. 25, 2974-2986
68. Jacobs, C. M., Boldingh, K. A., Slagsvold, H. H., Thoresen, G. H. & Paulsen, R. E. ERK2 prohibits apoptosis-induced subcellular translocation of orphan nuclear receptor NGFI-B/TR3 [J]. J. Biol. Chem. 2004. 279, 50097-50101
69. Castro-Obregon, S. et al. Alternative, nonapoptotic programmed cell death: mediation by arrestin 2, ERK2, and Nur77 [J]. J. Biol. Chem. 2004. 279, 17543-17553
70. Jacobs, C. M. & Paulsen, R. E. Crosstalk between ERK2 and RXR regulates nuclear import of transcription factor NGFI-B [J]. Biochem. Biophys. Res. Commun. 2005. 336, 646-652
71. Slagsvold, H. H., Ostvold, A. C., Fallgren, A. B. & Paulsen, R. E. Nuclear receptor and apoptosis initiator NGFI-B is a substrate for kinase ERK2 [J]. Biochem. Biophys. Res. Commun. 2002. 291, 1146-1150
72. Chen, H. Z. et al. Akt phosphorylates the TR3 orphan receptor and blocks its targeting to the mitochondria [J]. Carcinogenesis 2008. 29, 2078-2088
73. Pekarsky, Y. et al. Akt phosphorylates and regulates the orphan nuclear receptor Nur77 [J]. Proc. Natl. Acad. Sci. U. S. A 2001. 98, 3690-3694
74. Masuyama, N. et al. Akt inhibits the orphan nuclear receptor Nur77 and T-cell apoptosis [J]. J. Biol. Chem. 2001. 276, 32799-32805
75. Li, Y. & Lau, L. F. Adrenocorticotropic hormone regulates the activities of the orphan nuclear receptor Nur77 through modulation of phosphorylation [J]. Endocrinology 1997. 138, 4138-4146
76. Wingate, A. D., Campbell, D. G., Peggie, M. & Arthur, J. S. Nur77 is phosphorylated in cells by RSK in response to mitogenic stimulation [J]. Biochem. J. 2006. 393, 715-724
77. Wingate, A. D. & Arthur, J. S. Post-translational control of Nur77 [J]. Biochem. Soc. Trans. 2006. 34, 1107-1109
78. Hirata, Y., Kiuchi, K., Chen, H. C., Milbrandt, J. & Guroff, G. The phosphorylation and DNA binding of the DNA-binding domain of the orphan nuclear receptor NGFI-B [J]. J. Biol. Chem. 1993. 268, 24808-24812
79. Liu, B. et al. Regulation of the orphan receptor TR3 nuclear functions by c-Jun N terminal kinase phosphorylation [J]. Endocrinology 2007. 148, 34-44
80. Fujii, Y., Matsuda, S., Takayama, G. & Koyasu, S. ERK5 is involved in TCR-induced apoptosis through the modification of Nur77 [J]. Genes Cells 2008. 13, 411-419
81. Li, G. D. et al. Negative regulation of transcription coactivator p300 by orphan receptor TR3 [J]. Nucleic Acids Res. 2007. 35, 7348-7359
82. Lei Na-zi et al. A feedback regulatory loop between methyltransferase PRMT1 and orphan receptor TR3 [J]. Nucleic Acids Res. 2009. 37, 832-848
83. Wilson, T. E., Fahrner, T. J., Johnston, M. & Milbrandt, J. Identification of the DNA binding site for NGFI-B by genetic selection in yeast [J]. Science 1991. 252, 1296-1300
84. Philips, A. et al. Novel dimeric Nur77 signaling mechanism in endocrine and lymphoid cells [J]. Mol. Cell Biol. 1997. 17, 5946-5951
85. Perlmann, T. & Jansson, L. A novel pathway for vitamin A signaling mediated by RXR heterodimerization with NGFI-B and NURR1 [J]. Genes Dev. 1995. 9, 769-782
86. Levesque, D. & Rouillard, C. Nur77 and retinoid X receptors: crucial factors in dopamine-related neuroadaptation [J]. Trends Neurosci. 2007. 30, 22-30
87. Maruyama, K. et al. The NGFI-B subfamily of the nuclear receptor superfamily (review) [J]. Int. J. Oncol. 1998. 12, 1237-1243
88. Rajpal, A. et al. Transcriptional activation of known and novel apoptotic pathways by Nur77 orphan steroid receptor [J]. EMBO J. 2003. 22, 6526-6536
89. Maxwell, M. A. et al. Nur77 regulates lipolysis in skeletal muscle cells. Evidence for cross-talk between the

beta-adrenergic and an orphan nuclear hormone receptor pathway [J]. J. Biol. Chem. 2005. 280, 12573-12584
90. Chang, S. F. & Chung, B. C. Difference in transcriptional activity of two homologous CYP21A genes [J]. Mol. Endocrinol. 1995. 9, 1330-1336
91. Wilson, T. E., Mouw, A. R., Weaver, C. A., Milbrandt, J. & Parker, K. L. The orphan nuclear receptor NGFI-B regulates expression of the gene encoding steroid 21-hydroxylase [J]. Mol. Cell Biol. 1993. 13, 861-868
92. Stocco, C. O. et al. Prostaglandin F2alpha-induced expression of 20alpha-hydroxysteroid dehydrogenase involves the transcription factor NUR77 [J]. J. Biol. Chem. 2000. 275, 37202-37211
93. Martin, L. J. & Tremblay, J. J. The human 3beta-hydroxysteroid dehydrogenase/Delta5-Delta4 isomerase type 2 promoter is a novel target for the immediate early orphan nuclear receptor Nur77 in steroidogenic cells [J]. Endocrinology 2005. 146, 861-869
94. Robert, N. M., Martin, L. J. & Tremblay, J. J. The orphan nuclear receptor NR4A1 regulates insulin-like 3 gene transcription in Leydig cells [J]. Biol. Reprod. 2006. 74, 322-330
95. Song, K. H. et al. Orphan nuclear receptor Nur77 induces zinc finger protein GIOT-1 gene expression, and GIOT-1 acts as a novel corepressor of orphan nuclear receptor SF-1 via recruitment of HDAC2 [J]. J. Biol. Chem. 2006. 281, 15605-15614
96. Martin, L. J., Boucher, N., Brousseau, C. & Tremblay, J. J. The orphan nuclear receptor NUR77 regulates hormone-induced StAR transcription in Leydig cells through cooperation with Ca2+/calmodulin-dependent protein kinase I [J]. Mol. Endocrinol. 2008. 22, 2021-2037
97. Martin, L. J. & Tremblay, J. J. Glucocorticoids antagonize cAMP-induced Star transcription in Leydig cells through the orphan nuclear receptor NR4A1 [J]. J. Mol. Endocrinol. 2008. 41, 165-175
98. Chao, L. C. et al. Nur77 coordinately regulates expression of genes linked to glucose metabolism in skeletal muscle [J]. Mol. Endocrinol. 2007. 21, 2152-2163
99. Mu, X. & Chang, C. TR3 orphan nuclear receptor mediates apoptosis through up-regulating E2F1 in human prostate cancer LNCaP cells [J]. J. Biol. Chem. 2003. 278, 42840-42845
100. Gruber, F. et al. Direct binding of Nur77/NAK-1 to the plasminogen activator inhibitor 1 (PAI-1) promoter regulates TNF alpha -induced PAI-1 expression [J]. Blood 2003. 101, 3042-3048
101. Zhao, Y., Liu, Y. & Zheng, D. Alpha 1-antichymotrypsin/SerpinA3 is a novel target of orphan nuclear receptor Nur77 [J]. FEBS J. 2008. 275, 1025-1038
102. You, B., Jiang, Y. Y., Chen, S., Yan, G. & Sun, J. The Orphan Nuclear Receptor Nur77 Suppresses Endothelial Cell Activation Through Induction of I{kappa}B{alpha} Expression [J]. Circ. Res. 2009.
103. Chen, G. Q., Lin, B., Dawson, M. I. & Zhang, X. K. Nicotine modulates the effects of retinoids on growth inhibition and RAR beta expression in lung cancer cells [J]. Int. J. Cancer 2002. 99, 171-178
104. Wu, Q. et al. Inhibition of trans-retinoic acid-resistant human breast cancer cell growth by retinoid X receptor-selective retinoids [J]. Mol. Cell Biol. 1997. 17, 6598-6608
105. Batsche, E., Desroches, J., Bilodeau, S., Gauthier, Y. & Drouin, J. Rb enhances p160/SRC coactivator-dependent activity of nuclear receptors and hormone responsiveness [J]. J. Biol. Chem. 2005. 280, 19746-19756
106. Yeo, M. G., Yoo, Y. G., Choi, H. S., Pak, Y. K. & Lee, M. O. Negative cross-talk between Nur77 and small heterodimer partner and its role in apoptotic cell death of hepatoma cells [J]. Mol. Endocrinol. 2005. 19, 950-963

107. Hong, C. Y. et al. Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha [J]. Mol. Cell Biol. 2004. 24, 2593-2604
108. Park, K. C. et al. CR6-interacting factor 1 interacts with orphan nuclear receptor Nur77 and inhibits its transactivation [J]. Mol. Endocrinol. 2005. 19, 12-24
109. Kang, H. J. et al. Retinoic acid and its receptors repress the expression and transactivation functions of Nur77: a possible mechanism for the inhibition of apoptosis by retinoic acid [J]. Exp. Cell Res. 2000. 256, 545-554
110. Honkaniemi, J., Kononen, J., Kainu, T., Pyykonen, I. & Pelto-Huikko, M. Induction of multiple immediate early genes in rat hypothalamic paraventricular nucleus after stress [J]. Brain Res. Mol. Brain Res. 1994. 25, 234-

111. Murphy, E. P. & Conneely, O. M. Neuroendocrine regulation of the hypothalamic pituitary adrenal axis by the nurr1/nur77 subfamily of nuclear receptors [J]. Mol. Endocrinol. 1997. 11, 39-47
112. Lee, S. L. et al. Unimpaired thymic and peripheral T cell death in mice lacking the nuclear receptor NGFI-B (Nur77) [J]. Science 1995. 269, 532-535
113. Cheng, L. E., Chan, F. K., Cado, D. & Winoto, A. Functional redundancy of the Nur77 and Nor-1 orphan steroid receptors in T-cell apoptosis [J]. EMBO J. 1997. 16, 1865; C1997-1875
114. Gilbert, F. et al. Nur77 gene knockout alters dopamine neuron biochemical activity and dopamine turnover [J]. Biol. Psychiatry 2006. 60, 538-547
115. Fumoto, T., Yamaguchi, T., Hirose, F. & Osumi, T. Orphan nuclear receptor Nur77 accelerates the initial phase of adipocyte differentiation in 3T3-L1 cells by promoting mitotic clonal expansion [J]. J. Biochem. 2007. 141, 181-192
116. Wu, Q. et al. Modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and their heterodimerization [J]. EMBO J. 1997. 16, 1656-1669
117. Ke, N. et al. Nuclear hormone receptor NR4A2 is involved in cell transformation and apoptosis [J]. Cancer Res. 2004. 64, 8208-8212
118. Arkenbout, E. K. et al. Protective function of transcription factor TR3 orphan receptor in atherogenesis: decreased lesion formation in carotid artery ligation model in TR3 transgenic mice [J]. Circulation 2002. 106, 1530-1535
119. de, W., V et al. TR3 nuclear orphan receptor prevents cyclic stretch-induced proliferation of venous smooth muscle cells [J]. Am. J. Pathol. 2006. 168, 2027-2035
120. Arkenbout, E. K. et al. TR3 orphan receptor is expressed in vascular endothelial cells and mediates cell cycle arrest [J]. Arterioscler. Thromb. Vasc. Biol. 2003. 23, 1535-1540
121. Zeng, H. et al. Orphan nuclear receptor TR3/Nur77 regulates VEGF-A-induced angiogenesis through its transcriptional activity [J]. J. Exp. Med. 2006. 203, 719-729
122. Liu, Z. G., Smith, S. W., McLaughlin, K. A., Schwartz, L. M. & Osborne, B. A. Apoptotic signals delivered through the T-cell receptor of a T-cell hybrid require the immediate-early gene nur77 [J]. Nature 1994. 367, 281-284
123. Xue, Y. et al. Positive and negative thymic selection in T cell receptor-transgenic mice correlate with Nur77 mRNA expression [J]. Eur. J. Immunol. 1997. 27, 2048-2056
124. Jehn, B. M., Bielke, W., Pear, W. S. & Osborne, B. A. Cutting edge: protective effects of notch-1 on TCR-induced apoptosis [J]. J. Immunol. 1999. 162, 635-638
125. Young, C. Y., Murtha, P. E. & Zhang, J. Tumor-promoting phorbol ester-induced cell death and gene expression in a human prostate adenocarcinoma cell line [J]. Oncol. Res. 1994. 6, 203-210
126. Mullican, S. E. et al. Abrogation of nuclear receptors Nr4a3 and Nr4a1 leads to development of acute myeloid leukemia [J]. Nat. Med. 2007. 13, 730-735
127. Kuang, A. A., Cado, D. & Winoto, A. Nur77 transcription activity correlates with its apoptotic function in vivo [J]. Eur. J. Immunol. 1999. 29, 3722-3728
128. Cho, S. D. et al. Nur77 agonists induce proapoptotic genes and responses in colon cancer cells through nuclear receptor-dependent and nuclear receptor-independent pathways [J]. Cancer Res. 2007. 67, 674-683
129. Lin, X. F. et al. RXRalpha acts as a carrier for TR3 nuclear export in a 9-cis retinoic acid-dependent manner in gastric cancer cells [J]. J. Cell Sci. 2004. 117, 5609-5621
130. Lee, K. W. et al. Rapid apoptosis induction by IGFBP-3 involves an insulin-like growth factor-independent nucleomitochondrial translocation of RXRalpha/Nur77 [J]. J. Biol. Chem. 2005. 280, 16942-16948
131. Thompson, J. & Winoto, A. During negative selection, Nur77 family proteins translocate to mitochondria where they associate with Bcl-2 and expose its proapoptotic BH3 domain [J]. J. Exp. Med. 2008. 205, 1029-1036
132. Kolluri, S. K. et al. A short Nur77-derived peptide converts Bcl-2 from a protector to a killer [J]. Cancer Cell 2008. 14, 285-298

133. Luciano, F. et al. Nur77 converts phenotype of Bcl-B, an antiapoptotic protein expressed in plasma cells and myeloma [J]. Blood 2007. 109, 3849-3855
134. Wilson, A. J., Arango, D., Mariadason, J. M., Heerdt, B. G. & Augenlicht, L. H. TR3/Nur77 in colon cancer cell apoptosis [J]. Cancer Res. 2003. 63, 5401-5407
135. Liang, B. et al. Involvement of TR3/Nur77 translocation to the endoplasmic reticulum in ER stress-induced apoptosis [J]. Exp. Cell Res. 2007. 313, 2833-2844
136. Suzuki, S. et al. Nur77 as a survival factor in tumor necrosis factor signaling [J]. Proc. Natl. Acad. Sci. U. S. A 2003. 100, 8276-8280
137. de, L. L. & Denis, F. Inhibition of apoptosis by Nur77 through NF-kappaB activity modulation [J]. Cell Death. Differ. 2006. 13, 293-300
138. Fu, Y., Luo, L., Luo, N., Zhu, X. & Garvey, W. T. NR4A orphan nuclear receptors modulate insulin action and the glucose transport system: potential role in insulin resistance [J]. J. Biol. Chem. 2007. 282, 31525-31533
139. Maira, M., Martens, C., Philips, A. & Drouin, J. Heterodimerization between members of the Nur subfamily of orphan nuclear receptors as a novel mechanism for gene activation [J]. Mol. Cell Biol. 1999. 19, 7549; M1999-7557
140. Martens, C., Bilodeau, S., Maira, M., Gauthier, Y. & Drouin, J. Protein-protein interactions and transcriptional antagonism between the subfamily of NGFI-B/Nur77 orphan nuclear receptors and glucocorticoid receptor [J]. Mol. Endocrinol. 2005. 19, 885-897
141. Philips, A. et al. Antagonism between Nur77 and glucocorticoid receptor for control of transcription [J]. Mol. Cell Biol. 1997. 17, 5952-5959
142. Davis, I. J. & Lau, L. F. Endocrine and neurogenic regulation of the orphan nuclear receptors Nur77 and Nurr-1 in the adrenal glands [J]. Mol. Cell Biol. 1994. 14, 3469-3483
143. Havelock, J. C. et al. The NGFI-B family of transcription factors regulates expression of 3beta-hydroxysteroid dehydrogenase type 2 in the human ovary [J]. Mol. Hum. Reprod. 2005. 11, 79-85
144. Humphries, A., Weller, J., Klein, D., Baler, R. & Carter, D. A. NGFI-B (Nurr77/Nr4a1) orphan nuclear receptor in rat pinealocytes: circadian expression involves an adrenergic-cyclic AMP mechanism [J]. J. Neurochem. 2004. 91, 946-955
145. Bonta, P. I., Pols, T. W. & de Vries, C. J. NR4A nuclear receptors in atherosclerosis and vein-graft disease [J]. Trends Cardiovasc. Med. 2007. 17, 105-111
146. Harant, H. & Lindley, I. J. Negative cross-talk between the human orphan nuclear receptor Nur77/NAK-1/TR3 and nuclear factor-kappaB [J]. Nucleic Acids Res. 2004. 32, 5280-5290
147. Zhao, B. X. et al. p53 mediates the negative regulation of MDM2 by orphan receptor TR3 [J]. EMBO J. 2006. 25, 5703-5715
148. Kim, H. et al. A novel function of Nur77: physical and functional association with protein kinase C [J]. Biochem. Biophys. Res. Commun. 2006. 348, 950-956
149. Zetterstrom, R. H. et al. Dopamine neuron agenesis in Nurr1-deficient mice [J]. Science 1997. 276, 248-250

第二章

参 考 文 献

1. Brazil, D. P. & Hemmings, B. A. Ten years of protein kinase B signalling: a hard Akt to follow [J]. Trends Biochem. Sci. 2001. 26, 657-664
2. Bellacosa, A., Testa, J. R., Staal, S. P. & Tsichlis, P. N. A retroviral oncogene, akt, encoding a serine-threonine kinase containing an SH2-like region [J]. Science 1991. 254, 274-277
3. Hanada, M., Feng, J. & Hemmings, B. A. Structure, regulation and function of PKB/AKT--a major therapeutic target [J]. Biochim. Biophys. Acta 2004. 1697, 3-16
4. Datta, K. et al. AH/PH domain-mediated interaction between Akt molecules and its potential role in Akt regulation [J]. Mol. Cell Biol. 1995. 15, 2304-2310
5. Mayer, B. J., Ren, R., Clark, K. L. & Baltimore, D. A putative modular domain present in diverse signaling

proteins [J]. Cell 1993. 73, 629-630
6. Fayard, E., Tintignac, L. A., Baudry, A. & Hemmings, B. A. Protein kinase B/Akt at a glance [J]. J. Cell Sci. 2005. 118, 5675-5678
7. Foster, F. M., Traer, C. J., Abraham, S. M. & Fry, M. J. The phosphoinositide (PI) 3-kinase family [J]. J. Cell Sci. 2003. 116, 3037-3040
8. Wymann, M. P., Zvelebil, M. & Laffargue, M. Phosphoinositide 3-kinase signalling--which way to target? [J]. Trends Pharmacol. Sci. 2003. 24, 366-376
9. Vanhaesebroeck, B. & Alessi, D. R. The PI3K-PDK1 connection: more than just a road to PKB [J]. Biochem. J. 2000. 346 Pt 3, 561-576
10. Alessi, D. R. et al. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Balpha [J]. Curr. Biol. 1997. 7, 261-269
11. Stephens, L. et al. Protein kinase B kinases that mediate phosphatidylinositol 3,4,5-trisphosphate-dependent activation of protein kinase B [J]. Science 1998. 279, 710-714
12. Toker, A. & Newton, A. C. Akt/protein kinase B is regulated by autophosphorylation at the hypothetical PDK-2 site [J]. J. Biol. Chem. 2000. 275, 8271-8274
13. Balendran, A. et al. PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2 [J]. Curr. Biol. 1999. 9, 393-404
14. Persad, S. et al. Regulation of protein kinase B/Akt-serine 473 phosphorylation by integrin-linked kinase: critical roles for kinase activity and amino acids arginine 211 and serine 343 [J]. J. Biol. Chem. 2001. 276, 27462-27469
15. Alessi, D. R. et al. Mechanism of activation of protein kinase B by insulin and IGF-1 [J]. EMBO J. 1996. 15, 6541-6551
16. Kawakami, Y. et al. Protein kinase C betaII regulates Akt phosphorylation on Ser-473 in a cell type- and stimulus-specific fashion [J]. J. Biol. Chem. 2004. 279, 47720-47725
17. Feng, J., Park, J., Cron, P., Hess, D. & Hemmings, B. A. Identification of a PKB/Akt hydrophobic motif Ser-473 kinase as DNA-dependent protein kinase [J]. J. Biol. Chem. 2004. 279, 41189-41196
18. Viniegra, J. G. et al. Full activation of PKB/Akt in response to insulin or ionizing radiation is mediated through ATM [J]. J. Biol. Chem. 2005. 280, 4029-4036
19. Sarbassov, D. D., Guertin, D. A., Ali, S. M. & Sabatini, D. M. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex [J]. Science 2005. 307, 1098-1101
20. Yang, J. et al. Crystal structure of an activated Akt/protein kinase B ternary complex with GSK3-peptide and AMP-PNP [J]. Nat. Struct. Biol. 2002. 9, 940-944
21. Andjelkovic, M., Maira, S. M., Cron, P., Parker, P. J. & Hemmings, B. A. Domain swapping used to investigate the mechanism of protein kinase B regulation by 3-phosphoinositide-dependent protein kinase 1 and Ser473 kinase [J]. Mol. Cell Biol. 1999. 19, 5061-5072
22. Stambolic, V. et al. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN [J]. Cell 1998. 95, 29-39
23. Huber, M. et al. The role of SHIP in growth factor induced signalling [J]. Prog. Biophys. Mol. Biol. 1999. 71, 423-434
24. Andjelkovic, M. et al. Activation and phosphorylation of a pleckstrin homology domain containing protein kinase (RAC-PK/PKB) promoted by serum and protein phosphatase inhibitors [J]. Proc. Natl. Acad. Sci. U. S. A 1996. 93, 5699-5704
25. Gao, T., Furnari, F. & Newton, A. C. PHLPP: a phosphatase that directly dephosphorylates Akt, promotes apoptosis, and suppresses tumor growth [J]. Mol. Cell 2005. 18, 13-24
26. Cross, D. A., Alessi, D. R., Cohen, P., Andjelkovich, M. & Hemmings, B. A. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B [J]. Nature 1995. 378, 785-789
27. Alessi, D. R., Caudwell, F. B., Andjelkovic, M., Hemmings, B. A. & Cohen, P. Molecular basis for the substrate specificity of protein kinase B; comparison with MAPKAP kinase-1 and p70 S6 kinase [J]. FEBS Lett.

1996. 399, 333-338
28. Manning, B. D. & Cantley, L. C. AKT/PKB signaling: navigating downstream [J]. Cell 2007. 129, 1261-1274
29. Cho, H., Thorvaldsen, J. L., Chu, Q., Feng, F. & Birnbaum, M. J. Akt1/PKBalpha is required for normal growth but dispensable for maintenance of glucose homeostasis in mice [J]. J. Biol. Chem. 2001. 276, 38349-38352
30. Yang, Z. Z. et al. Protein kinase B alpha/Akt1 regulates placental development and fetal growth [J]. J. Biol. Chem. 2003. 278, 32124-32131
31. Chen, W. S. et al. Growth retardation and increased apoptosis in mice with homozygous disruption of the Akt1 gene [J]. Genes Dev. 2001. 15, 2203-2208
32. Yang, Z. Z. et al. Physiological functions of protein kinase B/Akt [J]. Biochem. Soc. Trans. 2004. 32, 350-354
33. Woulfe, D. et al. Defects in secretion, aggregation, and thrombus formation in platelets from mice lacking Akt2 [J]. J. Clin. Invest 2004. 113, 441-450
34. Easton, R. M. et al. Role for Akt3/protein kinase Bgamma in attainment of normal brain size [J]. Mol. Cell Biol. 2005. 25, 1869-1878
35. Tschopp, O. et al. Essential role of protein kinase B gamma (PKB gamma/Akt3) in postnatal brain development but not in glucose homeostasis [J]. Development 2005. 132, 2943-2954
36. Peng, X. D. et al. Dwarfism, impaired skin development, skeletal muscle atrophy, delayed bone development, and impeded adipogenesis in mice lacking Akt1 and Akt2 [J]. Genes Dev. 2003. 17, 1352-1365
37. Marte, B. M. & Downward, J. PKB/Akt: connecting phosphoinositide 3-kinase to cell survival and beyond [J]. Trends Biochem. Sci. 1997. 22, 355-358
38. Datta, S. R. et al. Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery [J]. Cell 1997. 91, 231-241
39. Datta, S. R. et al. 14-3-3 proteins and survival kinases cooperate to inactivate BAD by BH3 domain phosphorylation [J]. Mol. Cell 2000. 6, 41-51
40. Tran, H., Brunet, A., Griffith, E. C. & Greenberg, M. E. The many forks in FOXO's road [J]. Sci. STKE. 2003. 2003, RE5
41. Mayo, L. D. & Donner, D. B. A phosphatidylinositol 3-kinase/Akt pathway promotes translocation of Mdm2 from the cytoplasm to the nucleus [J]. Proc. Natl. Acad. Sci. U. S. A 2001. 98, 11598-11603
42. Zhou, B. P. et al. HER-2/neu induces p53 ubiquitination via Akt-mediated MDM2 phosphorylation [J]. Nat. Cell Biol. 2001. 3, 973-982
43. Pekarsky, Y. et al. Akt phosphorylates and regulates the orphan nuclear receptor Nur77 [J]. Proc. Natl. Acad. Sci. U. S. A 2001. 98, 3690-3694
44. Masuyama, N. et al. Akt inhibits the orphan nuclear receptor Nur77 and T-cell apoptosis [J]. J. Biol. Chem. 2001. 276, 32799-32805
45. Kim, A. H., Khursigara, G., Sun, X., Franke, T. F. & Chao, M. V. Akt phosphorylates and negatively regulates apoptosis signal-regulating kinase 1 [J]. Mol. Cell Biol. 2001. 21, 893-901
46. Ozes, O. N. et al. NF-kappaB activation by tumour necrosis factor requires the Akt serine-threonine kinase [J]. Nature 1999. 401, 82-85
47. Romashkova, J. A. & Makarov, S. S. NF-kappaB is a target of AKT in anti-apoptotic PDGF signalling [J]. Nature 1999. 401, 86-90
48. Plas, D. R. & Thompson, C. B. Akt-dependent transformation: there is more to growth than just surviving [J]. Oncogene 2005. 24, 7435-7442
49. Robey, R. B. & Hay, N. Mitochondrial hexokinases, novel mediators of the antiapoptotic effects of growth factors and Akt [J]. Oncogene 2006. 25, 4683-4696
50. Sabatini, D. M. mTOR and cancer: insights into a complex relationship [J]. Nat. Rev. Cancer 2006. 6, 729-734
51. Manning, B. D. & Cantley, L. C. Rheb fills a GAP between TSC and TOR [J]. Trends Biochem. Sci. 2003. 28, 573-576

52. Cai, S. L. et al. Activity of TSC2 is inhibited by AKT-mediated phosphorylation and membrane partitioning [J]. J. Cell Biol. 2006. 173, 279-289
53. Inoki, K., Li, Y., Zhu, T., Wu, J. & Guan, K. L. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling [J]. Nat. Cell Biol. 2002. 4, 648-657
54. Manning, B. D., Tee, A. R., Logsdon, M. N., Blenis, J. & Cantley, L. C. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway [J]. Mol. Cell 2002. 10, 151-162
55. Vander, H. E., Lee, S. I., Bandhakavi, S., Griffin, T. J. & Kim, D. H. Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40 [J]. Nat. Cell Biol. 2007. 9, 316-323
56. Berwick, D. C., Hers, I., Heesom, K. J., Moule, S. K. & Tavare, J. M. The identification of ATP-citrate lyase as a protein kinase B (Akt) substrate in primary adipocytes [J]. J. Biol. Chem. 2002. 277, 33895-33900
57. Liang, J. et al. PKB/Akt phosphorylates p27, impairs nuclear import of p27 and opposes p27-mediated G1 arrest [J]. Nat. Med. 2002. 8, 1153-1160
58. Shin, I. et al. PKB/Akt mediates cell-cycle progression by phosphorylation of p27(Kip1) at threonine 157 and modulation of its cellular localization [J]. Nat. Med. 2002. 8, 1145-1152
59. Medema, R. H., Kops, G. J., Bos, J. L. & Burgering, B. M. AFX-like Forkhead transcription factors mediate cell-cycle regulation by Ras and PKB through p27kip1 [J]. Nature 2000. 404, 782-787
60. Zhou, B. P. et al. Cytoplasmic localization of p21Cip1/WAF1 by Akt-induced phosphorylation in HER-2/neu-overexpressing cells [J]. Nat. Cell Biol. 2001. 3, 245-252
61. King, F. W., Skeen, J., Hay, N. & Shtivelman, E. Inhibition of Chk1 by activated PKB/Akt [J]. Cell Cycle 2004. 3, 634-637
62. Puc, J. et al. Lack of PTEN sequesters CHK1 and initiates genetic instability [J]. Cancer Cell 2005. 7, 193-204
63. Diehl, J. A., Cheng, M., Roussel, M. F. & Sherr, C. J. Glycogen synthase kinase-3beta regulates cyclin D1 proteolysis and subcellular localization [J]. Genes Dev. 1998. 12, 3499-3511
64. Wei, W., Jin, J., Schlisio, S., Harper, J. W. & Kaelin, W. G., Jr. The v-Jun point mutation allows c-Jun to escape GSK3-dependent recognition and destruction by the Fbw7 ubiquitin ligase [J]. Cancer Cell 2005. 8, 25-33

65. Welcker, M. et al. Multisite phosphorylation by Cdk2 and GSK3 controls cyclin E degradation [J]. Mol. Cell 2003. 12, 381-392
66. Yeh, E. et al. A signalling pathway controlling c-Myc degradation that impacts oncogenic transformation of human cells [J]. Nat. Cell Biol. 2004. 6, 308-318
67. Calera, M. R. et al. Insulin increases the association of Akt-2 with Glut4-containing vesicles [J]. J. Biol. Chem. 1998. 273, 7201-7204
68. Bai, L. et al. Dissecting multiple steps of GLUT4 trafficking and identifying the sites of insulin action [J]. Cell Metab 2007. 5, 47-57
69. Lum, J. J. et al. The transcription factor HIF-1alpha plays a critical role in the growth factor-dependent regulation of both aerobic and anaerobic glycolysis [J]. Genes Dev. 2007. 21, 1037-1049
70. Majumder, P. K. et al. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways [J]. Nat. Med. 2004. 10, 594-601
71. Elstrom, R. L. et al. Akt stimulates aerobic glycolysis in cancer cells [J]. Cancer Res. 2004. 64, 3892-3899
72. Sundqvist, A. et al. Control of lipid metabolism by phosphorylation-dependent degradation of the SREBP family of transcription factors by SCF(Fbw7) [J]. Cell Metab 2005. 1, 379-391
73. Olsson, A. K., Dimberg, A., Kreuger, J. & Claesson-Welsh, L. VEGF receptor signalling - in control of vascular function [J]. Nat. Rev. Mol. Cell Biol. 2006. 7, 359-371
74. Dimmeler, S. et al. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation [J]. Nature 1999. 399, 601-605
75. Fulton, D. et al. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt [J]. Nature 1999. 399, 597-601

76. Gordan, J. D. & Simon, M. C. Hypoxia-inducible factors: central regulators of the tumor phenotype [J]. Curr. Opin. Genet. Dev. 2007. 17, 71-77
77. Semenza, G. L. Targeting HIF-1 for cancer therapy [J]. Nat. Rev. Cancer 2003. 3, 721-732
78. Irie, H. Y. et al. Distinct roles of Akt1 and Akt2 in regulating cell migration and epithelial-mesenchymal transition [J]. J. Cell Biol. 2005. 171, 1023-1034
79. Yoeli-Lerner, M. et al. Akt blocks breast cancer cell motility and invasion through the transcription factor NFAT [J]. Mol. Cell 2005. 20, 539-550
80. Hutchinson, J. N., Jin, J., Cardiff, R. D., Woodgett, J. R. & Muller, W. J. Activation of Akt-1 (PKB-alpha) can accelerate ErbB-2-mediated mammary tumorigenesis but suppresses tumor invasion [J]. Cancer Res. 2004. 64, 3171-3178
81. Arboleda, M. J. et al. Overexpression of AKT2/protein kinase Bbeta leads to up-regulation of beta1 integrins, increased invasion, and metastasis of human breast and ovarian cancer cells [J]. Cancer Res. 2003. 63, 196-206
82. Zhou, G. L. et al. Opposing roles for Akt1 and Akt2 in Rac/Pak signaling and cell migration [J]. J. Biol. Chem. 2006. 281, 36443-36453
83. Luo, Y. et al. Potent and selective inhibitors of Akt kinases slow the progress of tumors in vivo [J]. Mol. Cancer Ther. 2005. 4, 977-986
84. Li, H. et al. Cytochrome c release and apoptosis induced by mitochondrial targeting of nuclear orphan receptor TR3 [J]. Science 2000. 289, 1159-1164
85. del, P. L., Gonzalez-Garcia, M., Page, C., Herrera, R. & Nunez, G. Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt [J]. Science 1997. 278, 687-689
86. Shtutman, M. et al. The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway [J]. Proc. Natl. Acad. Sci. U. S. A 1999. 96, 5522-5527
87. Liu, S. et al. Induction of apoptosis by TPA and VP-16 is through translocation of TR3 [J]. World J. Gastroenterol. 2002. 8, 446-450
88. Cao, X. et al. Retinoid X receptor regulates Nur77/TR3-dependent apoptosis [corrected] by modulating its nuclear export and mitochondrial targeting [J]. Mol. Cell Biol. 2004. 24, 9705-9725
89. Wu, Q., Liu, S., Ye, X. F., Huang, Z. W. & Su, W. J. Dual roles of Nur77 in selective regulation of apoptosis and cell cycle by TPA and ATRA in gastric cancer cells [J]. Carcinogenesis 2002. 23, 1583-1592
90. Han, Y. H. et al. Regulation of Nur77 nuclear export by c-Jun N-terminal kinase and Akt [J]. Oncogene 2006. 25, 2974-2986
91. Lin, B. et al. Conversion of Bcl-2 from protector to killer by interaction with nuclear orphan receptor Nur77/TR3 [J]. Cell 2004. 116, 527-540
92. Reed, J. C. Bcl-2-family proteins and hematologic malignancies: history and future prospects [J]. Blood 2008. 111, 3322-3330
93. Nicholson, K. M. & Anderson, N. G. The protein kinase B/Akt signalling pathway in human malignancy [J]. Cell Signal. 2002. 14, 381-395
94. Zhou, H., Li, X. M., Meinkoth, J. & Pittman, R. N. Akt regulates cell survival and apoptosis at a postmitochondrial level [J]. J. Cell Biol. 2000. 151, 483-494
95. Yamaguchi, H. & Wang, H. G. The protein kinase PKB/Akt regulates cell survival and apoptosis by inhibiting Bax conformational change [J]. Oncogene 2001. 20, 7779-7786
96. Cardone, M. H. et al. Regulation of cell death protease caspase-9 by phosphorylation [J]. Science 1998. 282, 1318-1321
97. Zhou, T. et al. Inhibition of Nur77/Nurr1 leads to inefficient clonal deletion of self-reactive T cells [J]. J. Exp. Med. 1996. 183, 1879-1892
98. Calnan, B. J., Szychowski, S., Chan, F. K., Cado, D. & Winoto, A. A role for the orphan steroid receptor Nur77 in apoptosis accompanying antigen-induced negative selection [J]. Immunity. 1995. 3, 273-282
99. Kuang, A. A., Cado, D. & Winoto, A. Nur77 transcription activity correlates with its apoptotic function in vivo [J]. Eur. J. Immunol. 1999. 29, 3722-3728

100. Katagiri, Y. et al. Modulation of retinoid signalling through NGF-induced nuclear export of NGFI-B [J]. Nat. Cell Biol. 2000. 2, 435-440
101. Jacobs, C. M., Boldingh, K. A., Slagsvold, H. H., Thoresen, G. H. & Paulsen, R. E. ERK2 prohibits apoptosis-induced subcellular translocation of orphan nuclear receptor NGFI-B/TR3 [J]. J. Biol. Chem. 2004. 279, 50097-50101
102. Jacobs, C. M. & Paulsen, R. E. Crosstalk between ERK2 and RXR regulates nuclear import of transcription factor NGFI-B [J]. Biochem. Biophys. Res. Commun. 2005. 336, 646-652
103. Castro-Obregon, S. et al. Alternative, nonapoptotic programmed cell death: mediation by arrestin 2, ERK2, and Nur77 [J]. J. Biol. Chem. 2004. 279, 17543-17553
104. Lee, K. W. et al. Contribution of the orphan nuclear receptor Nur77 to the apoptotic action of IGFBP-3 [J]. Carcinogenesis 2007. 28, 1653-1658
105. Bellacosa, A. et al. Akt activation by growth factors is a multiple-step process: the role of the PH domain [J]. Oncogene 1998. 17, 313-325
106. Chan, T. O., Rittenhouse, S. E. & Tsichlis, P. N. AKT/PKB and other D3 phosphoinositide-regulated kinases: kinase activation by phosphoinositide-dependent phosphorylation [J]. Annu. Rev. Biochem. 1999. 68, 965-1014
107. Ahmed, N. N. et al. The proteins encoded by c-akt and v-akt differ in post-translational modification, subcellular localization and oncogenic potential [J]. Oncogene 1993. 8, 1957-1963

第三章
参 考 文 献

1. Pawson, T. & Scott, J. D. Protein phosphorylation in signaling--50 years and counting [J]. Trends Biochem. Sci. 2005. 30, 286-290
2. Blume-Jensen, P. & Hunter, T. Oncogenic kinase signalling [J]. Nature 2001. 411, 355-365
3. Fischer, G. & Aumuller, T. Regulation of peptide bond cis/trans isomerization by enzyme catalysis and its implication in physiological processes [J]. Rev. Physiol Biochem. Pharmacol. 2003. 148, 105-150
4. Galat, A. Peptidylprolyl cis/trans isomerases (immunophilins): biological diversity--targets--functions [J]. Curr. Top. Med. Chem. 2003. 3, 1315-1347
5. Nigg, E. A. Mitotic kinases as regulators of cell division and its checkpoints [J]. Nat. Rev. Mol. Cell Biol. 2001. 2, 21-32
6. Lu, K. P., Liou, Y. C. & Vincent, I. Proline-directed phosphorylation and isomerization in mitotic regulation and in Alzheimer's Disease [J]. Bioessays 2003. 25, 174-181
7. Lu, K. P., Hanes, S. D. & Hunter, T. A human peptidyl-prolyl isomerase essential for regulation of mitosis [J]. Nature 1996. 380, 544-547
8. Yeh, E. S. & Means, A. R. PIN1, the cell cycle and cancer [J]. Nat. Rev. Cancer 2007. 7, 381-388
9. Ryo, A., Liou, Y. C., Lu, K. P. & Wulf, G. Prolyl isomerase Pin1: a catalyst for oncogenesis and a potential therapeutic target in cancer [J]. J. Cell Sci. 2003. 116, 773-783
10. Lu, P. J., Zhou, X. Z., Shen, M. & Lu, K. P. Function of WW domains as phosphoserine- or phosphothreonine-binding modules [J]. Science 1999. 283, 1325-1328
11. Ranganathan, R., Lu, K. P., Hunter, T. & Noel, J. P. Structural and functional analysis of the mitotic rotamase Pin1 suggests substrate recognition is phosphorylation dependent [J]. Cell 1997. 89, 875-886
12. Zhou, X. Z. et al. Pin1-dependent prolyl isomerization regulates dephosphorylation of Cdc25C and tau proteins [J]. Mol. Cell 2000. 6, 873-883
13. Yaffe, M. B. et al. Sequence-specific and phosphorylation-dependent proline isomerization: a potential mitotic regulatory mechanism [J]. Science 1997. 278, 1957-1960
14. Verdecia, M. A., Bowman, M. E., Lu, K. P., Hunter, T. & Noel, J. P. Structural basis for phosphoserine-proline recognition by group IV WW domains [J]. Nat. Struct. Biol. 2000. 7, 639-643

15. Pastorino, L. et al. The prolyl isomerase Pin1 regulates amyloid precursor protein processing and amyloid-beta production [J]. Nature 2006. 440, 528-534
16. Jacobs, D. M. et al. Peptide binding induces large scale changes in inter-domain mobility in human Pin1 [J]. J. Biol. Chem. 2003. 278, 26174-26182
17. Hennig, L. et al. Selective inactivation of parvulin-like peptidyl-prolyl cis/trans isomerases by juglone [J]. Biochemistry 1998. 37, 5953-5960
18. Chao, S. H., Greenleaf, A. L. & Price, D. H. Juglone, an inhibitor of the peptidyl-prolyl isomerase Pin1, also directly blocks transcription [J]. Nucleic Acids Res. 2001. 29, 767-773
19. Bao, L. et al. Prevalent overexpression of prolyl isomerase Pin1 in human cancers [J]. Am. J. Pathol. 2004. 164, 1727-1737
20. Atchison, F. W., Capel, B. & Means, A. R. Pin1 regulates the timing of mammalian primordial germ cell proliferation [J]. Development 2003. 130, 3579-3586
21. Ryo, A. et al. PIN1 is an E2F target gene essential for Neu/Ras-induced transformation of mammary epithelial cells [J]. Mol. Cell Biol. 2002. 22, 5281-5295
22. Wulf, G. M. et al. Pin1 is overexpressed in breast cancer and cooperates with Ras signaling in increasing the transcriptional activity of c-Jun towards cyclin D1 [J]. EMBO J. 2001. 20, 3459-3472
23. Rustighi, A. et al. The prolyl-isomerase Pin1 is a Notch1 target that enhances Notch1 activation in cancer [J]. Nat. Cell Biol. 2009. 11, 133-142
24. MacLachlan, T. K. et al. BRCA1 effects on the cell cycle and the DNA damage response are linked to altered gene expression [J]. J. Biol. Chem. 2000. 275, 2777-2785
25. Lu, P. J., Zhou, X. Z., Liou, Y. C., Noel, J. P. & Lu, K. P. Critical role of WW domain phosphorylation in regulating phosphoserine binding activity and Pin1 function [J]. J. Biol. Chem. 2002. 277, 2381-2384
26. Rippmann, J. F. et al. Phosphorylation-dependent proline isomerization catalyzed by Pin1 is essential for tumor cell survival and entry into mitosis [J]. Cell Growth Differ. 2000. 11, 409-416
27. Eckerdt, F. et al. Polo-like kinase 1-mediated phosphorylation stabilizes Pin1 by inhibiting its ubiquitination in human cells [J]. J. Biol. Chem. 2005. 280, 36575-36583
28. Sultana, R. et al. Oxidative modification and down-regulation of Pin1 in Alzheimer's disease hippocampus: A redox proteomics analysis [J]. Neurobiol. Aging 2006. 27, 918-925
29. Butterfield, D. A. et al. Redox proteomics identification of oxidatively modified hippocampal proteins in mild cognitive impairment: insights into the development of Alzheimer's disease [J]. Neurobiol. Dis. 2006. 22, 223-232
30. Orlicky, S., Tang, X., Willems, A., Tyers, M. & Sicheri, F. Structural basis for phosphodependent substrate selection and orientation by the SCFCdc4 ubiquitin ligase [J]. Cell 2003. 112, 243-256
31. Weiwad, M., Kullertz, G., Schutkowski, M. & Fischer, G. Evidence that the substrate backbone conformation is critical to phosphorylation by p42 MAP kinase [J]. FEBS Lett. 2000. 478, 39-42
32. Brown, N. R., Noble, M. E., Endicott, J. A. & Johnson, L. N. The structural basis for specificity of substrate and recruitment peptides for cyclin-dependent kinases [J]. Nat. Cell Biol. 1999. 1, 438-443
33. Lu, K. P. & Zhou, X. Z. The prolyl isomerase PIN1: a pivotal new twist in phosphorylation signalling and disease [J]. Nat. Rev. Mol. Cell Biol. 2007. 8, 904-916
34. Shen, M., Stukenberg, P. T., Kirschner, M. W. & Lu, K. P. The essential mitotic peptidyl-prolyl isomerase Pin1 binds and regulates mitosis-specific phosphoproteins [J]. Genes Dev. 1998. 12, 706-720
35. Crenshaw, D. G., Yang, J., Means, A. R. & Kornbluth, S. The mitotic peptidyl-prolyl isomerase, Pin1, interacts with Cdc25 and Plx1 [J]. EMBO J. 1998. 17, 1315-1327
36. Winkler, K. E., Swenson, K. I., Kornbluth, S. & Means, A. R. Requirement of the prolyl isomerase Pin1 for the replication checkpoint [J]. Science 2000. 287, 1644-1647
37. Stukenberg, P. T. & Kirschner, M. W. Pin1 acts catalytically to promote a conformational change in Cdc25 [J]. Mol. Cell 2001. 7, 1071-1083
38. Xu, Y. X. & Manley, J. L. The prolyl isomerase Pin1 functions in mitotic chromosome condensation [J]. Mol.

Cell 2007. 26, 287-300
39. Ryo, A., Nakamura, M., Wulf, G., Liou, Y. C. & Lu, K. P. Pin1 regulates turnover and subcellular localization of beta-catenin by inhibiting its interaction with APC [J]. Nat. Cell Biol. 2001. 3, 793-801
40. Ryo, A. et al. Regulation of NF-kappaB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA [J]. Mol. Cell 2003. 12, 1413-1426
41. Chen, S. Y. et al. Activation of beta-catenin signaling in prostate cancer by peptidyl-prolyl isomerase Pin1-mediated abrogation of the androgen receptor-beta-catenin interaction [J]. Mol. Cell Biol. 2006. 26, 929-939
42. Liou, Y. C. et al. Loss of Pin1 function in the mouse causes phenotypes resembling cyclin D1-null phenotypes [J]. Proc. Natl. Acad. Sci. U. S. A 2002. 99, 1335-1340
43. Wulf, G., Garg, P., Liou, Y. C., Iglehart, D. & Lu, K. P. Modeling breast cancer in vivo and ex vivo reveals an essential role of Pin1 in tumorigenesis [J]. EMBO J. 2004. 23, 3397-3407
44. Yu, Q., Geng, Y. & Sicinski, P. Specific protection against breast cancers by cyclin D1 ablation [J]. Nature 2001. 411, 1017-1021
45. Suizu, F., Ryo, A., Wulf, G., Lim, J. & Lu, K. P. Pin1 regulates centrosome duplication, and its overexpression induces centrosome amplification, chromosome instability, and oncogenesis [J]. Mol. Cell Biol. 2006. 26, 1463-1479
46. Pang, R. et al. PIN1 overexpression and beta-catenin gene mutations are distinct oncogenic events in human hepatocellular carcinoma [J]. Oncogene 2004. 23, 4182-4186
47. Yeh, E. S., Lew, B. O. & Means, A. R. The loss of PIN1 deregulates cyclin E and sensitizes mouse embryo fibroblasts to genomic instability [J]. J. Biol. Chem. 2006. 281, 241-251
48. Wulf, G. M., Liou, Y. C., Ryo, A., Lee, S. W. & Lu, K. P. Role of Pin1 in the regulation of p53 stability and p21 transactivation, and cell cycle checkpoints in response to DNA damage [J]. J. Biol. Chem. 2002. 277, 47976-47979
49. Zheng, H. et al. The prolyl isomerase Pin1 is a regulator of p53 in genotoxic response [J]. Nature 2002. 419, 849-853
50. Zacchi, P. et al. The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults [J]. Nature 2002. 419, 853-857
51. Mantovani, F. et al. The prolyl isomerase Pin1 orchestrates p53 acetylation and dissociation from the apoptosis inhibitor iASPP [J]. Nat. Struct. Mol. Biol. 2007. 14, 912-920
52. Mantovani, F. et al. Pin1 links the activities of c-Abl and p300 in regulating p73 function [J]. Mol. Cell 2004. 14, 625-636
53. De, N. F. et al. The prolyl isomerase Pin1 affects Che-1 stability in response to apoptotic DNA damage [J]. J. Biol. Chem. 2007. 282, 19685-19691
54. Pinton, P. et al. Protein kinase C beta and prolyl isomerase 1 regulate mitochondrial effects of the life-span determinant p66Shc [J]. Science 2007. 315, 659-663
55. Shen, Z. J., Esnault, S., Schinzel, A., Borner, C. & Malter, J. S. The peptidyl-prolyl isomerase Pin1 facilitates cytokine-induced survival of eosinophils by suppressing Bax activation [J]. Nat. Immunol. 2009.
56. Ryo, A. et al. A suppressive role of the prolyl isomerase Pin1 in cellular apoptosis mediated by the death-associated protein Daxx [J]. J. Biol. Chem. 2007. 282, 36671-36681
57. Reineke, E. L. et al. Degradation of the tumor suppressor PML by Pin1 contributes to the cancer phenotype of breast cancer MDA-MB-231 cells [J]. Mol. Cell Biol. 2008. 28, 997-1006
58. Lee, T. H. et al. Essential role of Pin1 in the regulation of TRF1 stability and telomere maintenance [J]. Nat. Cell Biol. 2009. 11, 97-105
59. Lu, P. J., Wulf, G., Zhou, X. Z., Davies, P. & Lu, K. P. The prolyl isomerase Pin1 restores the function of Alzheimer-associated phosphorylated tau protein [J]. Nature 1999. 399, 784-788
60. Hamdane, M. et al. Pin1 allows for differential Tau dephosphorylation in neuronal cells [J]. Mol. Cell Neurosci. 2006. 32, 155-160
61. Butterfield, D. A. et al. Pin1 in Alzheimer's disease [J]. J. Neurochem. 2006. 98, 1697-1706

62. Akiyama, H., Shin, R. W., Uchida, C., Kitamoto, T. & Uchida, T. Pin1 promotes production of Alzheimer's amyloid beta from beta-cleaved amyloid precursor protein [J]. Biochem. Biophys. Res. Commun. 2005. 336, 521-529
63. Liou, Y. C. et al. Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration [J]. Nature 2003. 424, 556-561
64. Esnault, S. et al. Pin1 modulates the type 1 immune response [J]. PLoS. ONE. 2007. 2, e226
65. Esnault, S., Shen, Z. J., Whitesel, E. & Malter, J. S. The peptidyl-prolyl isomerase Pin1 regulates granulocyte-macrophage colony-stimulating factor mRNA stability in T lymphocytes [J]. J. Immunol. 2006. 177, 6999-7006
66. Yao, J. L., Kops, O., Lu, P. J. & Lu, K. P. Functional conservation of phosphorylation-specific prolyl isomerases in plants [J]. J. Biol. Chem. 2001. 276, 13517-13523
67. Zhu, J. X., Dagostino, E., Rejto, P. A., Mroczkowski, B. & Murray, B. Identification and characterization of a novel and functional murine Pin1 isoform [J]. Biochem. Biophys. Res. Commun. 2007. 359, 529-535
68. Katagiri, Y. et al. Modulation of retinoid signalling through NGF-induced nuclear export of NGFI-B [J]. Nat. Cell Biol. 2000. 2, 435-440
69. Liu, B. et al. Regulation of the orphan receptor TR3 nuclear functions by c-Jun N terminal kinase phosphorylation [J]. Endocrinology 2007. 148, 34-44
70. Jacobs, C. M., Boldingh, K. A., Slagsvold, H. H., Thoresen, G. H. & Paulsen, R. E. ERK2 prohibits apoptosis-induced subcellular translocation of orphan nuclear receptor NGFI-B/TR3 [J]. J. Biol. Chem. 2004. 279, 50097-50101
71. Mauro, A. et al. PKCalpha-mediated ERK, JNK and p38 activation regulates the myogenic program in human rhabdomyosarcoma cells [J]. J. Cell Sci. 2002. 115, 3587-3599
72. Castro-Obregon, S. et al. Alternative, nonapoptotic programmed cell death: mediation by arrestin 2, ERK2, and Nur77 [J]. J. Biol. Chem. 2004. 279, 17543-17553
73. Wingate, A. D., Campbell, D. G., Peggie, M. & Arthur, J. S. Nur77 is phosphorylated in cells by RSK in response to mitogenic stimulation [J]. Biochem. J. 2006. 393, 715-724
74. Wansa, K. D., Harris, J. M. & Muscat, G. E. The activation function-1 domain of Nur77/NR4A1 mediates trans-activation, cell specificity, and coactivator recruitment [J]. J. Biol. Chem. 2002. 277, 33001-33011
75. Maira, M., Martens, C., Batsche, E., Gauthier, Y. & Drouin, J. Dimer-specific potentiation of NGFI-B (Nur77) transcriptional activity by the protein kinase A pathway and AF-1-dependent coactivator recruitment [J]. Mol. Cell Biol. 2003. 23, 763-776
76. Martin, L. J. & Tremblay, J. J. The human 3beta-hydroxysteroid dehydrogenase/Delta5-Delta4 isomerase type 2 promoter is a novel target for the immediate early orphan nuclear receptor Nur77 in steroidogenic cells [J]. Endocrinology 2005. 146, 861-869
77. Kolluri, S. K. et al. Mitogenic effect of orphan receptor TR3 and its regulation by MEKK1 in lung cancer cells [J]. Mol. Cell Biol. 2003. 23, 8651-8667
78. Pei, L., Castrillo, A. & Tontonoz, P. Regulation of macrophage inflammatory gene expression by the orphan nuclear receptor Nur77 [J]. Mol. Endocrinol. 2006. 20, 786-794
79. Ryo, A. et al. Stable suppression of tumorigenicity by Pin1-targeted RNA interference in prostate cancer [J]. Clin. Cancer Res. 2005. 11, 7523-7531
80. Moll, U. M., Marchenko, N. & Zhang, X. K. p53 and Nur77/ [J]. Oncogene 2006. 25, 4725-4743
81. Berger, M., Stahl, N., Del, S. G. & Haupt, Y. Mutations in proline 82 of p53 impair its activation by Pin1 and Chk2 in response to DNA damage [J]. Mol. Cell Biol. 2005. 25, 5380-5388
82. Brondani, V., Schefer, Q., Hamy, F. & Klimkait, T. The peptidyl-prolyl isomerase Pin1 regulates phospho-Ser77 retinoic acid receptor alpha stability [J]. Biochem. Biophys. Res. Commun. 2005. 328, 6-13
83. Minden, A. et al. Differential activation of ERK and JNK mitogen-activated protein kinases by Raf-1 and MEKK [J]. Science 1994. 266, 1719-1723

参 考 文 献

1. Nusse, R. & Varmus, H. E. Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome [J]. Cell 1982. 31, 99-109
2. Nusslein-Volhard, C. & Wieschaus, E. Mutations affecting segment number and polarity in Drosophila [J]. Nature 1980. 287, 795-801
3. Rijsewijk, F. et al. The Drosophila homolog of the mouse mammary oncogene int-1 is identical to the segment polarity gene wingless [J]. Cell 1987. 50, 649-657
4. Noordermeer, J., Klingensmith, J., Perrimon, N. & Nusse, R. dishevelled and armadillo act in the wingless signalling pathway in Drosophila [J]. Nature 1994. 367, 80-83
5. Dominguez, I., Itoh, K. & Sokol, S. Y. Role of glycogen synthase kinase 3 beta as a negative regulator of dorsoventral axis formation in Xenopus embryos [J]. Proc. Natl. Acad. Sci. U. S. A 1995. 92, 8498-8502
6. Guger, K. A. & Gumbiner, B. M. beta-Catenin has Wnt-like activity and mimics the Nieuwkoop signaling center in Xenopus dorsal-ventral patterning [J]. Dev. Biol. 1995. 172, 115-125
7. He, X., Saint-Jeannet, J. P., Woodgett, J. R., Varmus, H. E. & Dawid, I. B. Glycogen synthase kinase-3 and dorsoventral patterning in Xenopus embryos [J]. Nature 1995. 374, 617-622
8. Huelsken, J. & Behrens, J. The Wnt signalling pathway [J]. J. Cell Sci. 2002. 115, 3977-3978
9. Du, S. J., Purcell, S. M., Christian, J. L., McGrew, L. L. & Moon, R. T. Identification of distinct classes and functional domains of Wnts through expression of wild-type and chimeric proteins in Xenopus embryos [J]. Mol. Cell Biol. 1995. 15, 2625-2634
10. Willert, K. et al. Wnt proteins are lipid-modified and can act as stem cell growth factors [J]. Nature 2003. 423, 448-452
11. Zhai, L., Chaturvedi, D. & Cumberledge, S. Drosophila wnt-1 undergoes a hydrophobic modification and is targeted to lipid rafts, a process that requires porcupine [J]. J. Biol. Chem. 2004. 279, 33220-33227
12. Banziger, C. et al. Wntless, a conserved membrane protein dedicated to the secretion of Wnt proteins from signaling cells [J]. Cell 2006. 125, 509-522
13. Bartscherer, K., Pelte, N., Ingelfinger, D. & Boutros, M. Secretion of Wnt ligands requires Evi, a conserved transmembrane protein [J]. Cell 2006. 125, 523-533
14. Coudreuse, D. Y., Roel, G., Betist, M. C., Destree, O. & Korswagen, H. C. Wnt gradient formation requires retromer function in Wnt-producing cells [J]. Science 2006. 312, 921-924
15. Panakova, D., Sprong, H., Marois, E., Thiele, C. & Eaton, S. Lipoprotein particles are required for Hedgehog and Wingless signalling [J]. Nature 2005. 435, 58-65
16. Hsieh, J. C., Rattner, A., Smallwood, P. M. & Nathans, J. Biochemical characterization of Wnt-frizzled interactions using a soluble, biologically active vertebrate Wnt protein [J]. Proc. Natl. Acad. Sci. U. S. A 1999. 96, 3546-3551
17. Rulifson, E. J., Wu, C. H. & Nusse, R. Pathway specificity by the bifunctional receptor frizzled is determined by affinity for wingless [J]. Mol. Cell 2000. 6, 117-126
18. Cadigan, K. M., Fish, M. P., Rulifson, E. J. & Nusse, R. Wingless repression of Drosophila frizzled 2 expression shapes the Wingless morphogen gradient in the wing [J]. Cell 1998. 93, 767-777
19. Zhang, J. & Carthew, R. W. Interactions between Wingless and DFz2 during Drosophila wing development [J]. Development 1998. 125, 3075-3085
20. He, X., Semenov, M., Tamai, K. & Zeng, X. LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way [J]. Development 2004. 131, 1663-1677
21. Wehrli, M. et al. arrow encodes an LDL-receptor-related protein essential for Wingless signalling [J]. Nature 2000. 407, 527-530
22. Pinson, K. I., Brennan, J., Monkley, S., Avery, B. J. & Skarnes, W. C. An LDL-receptor-related protein mediates Wnt signalling in mice [J]. Nature 2000. 407, 535-538
23. Kelly, O. G., Pinson, K. I. & Skarnes, W. C. The Wnt co-receptors Lrp5 and Lrp6 are essential for

gastrulation in mice [J]. Development 2004. 131, 2803-2815
24. Liu, P. et al. Requirement for Wnt3 in vertebrate axis formation [J]. Nat. Genet. 1999. 22, 361-365
25. Huelsken, J. et al. Requirement for beta-catenin in anterior-posterior axis formation in mice [J]. J. Cell Biol. 2000. 148, 567-578
26. Tamai, K. et al. LDL-receptor-related proteins in Wnt signal transduction [J]. Nature 2000. 407, 530-535
27. Semenov, M. V. et al. Head inducer Dickkopf-1 is a ligand for Wnt coreceptor LRP6 [J]. Curr. Biol. 2001. 11, 951-961
28. Cong, F., Schweizer, L. & Varmus, H. Wnt signals across the plasma membrane to activate the beta-catenin pathway by forming oligomers containing its receptors, Frizzled and LRP [J]. Development 2004. 131, 5103-5115
29. Willert, K. & Jones, K. A. Wnt signaling: is the party in the nucleus? [J]. Genes Dev. 2006. 20, 1394-1404
30. Peifer, M., McCrea, P. D., Green, K. J., Wieschaus, E. & Gumbiner, B. M. The vertebrate adhesive junction proteins beta-catenin and plakoglobin and the Drosophila segment polarity gene armadillo form a multigene family with similar properties [J]. J. Cell Biol. 1992. 118, 681-691
31. Aberle, H., Bauer, A., Stappert, J., Kispert, A. & Kemler, R. beta-catenin is a target for the ubiquitin-proteasome pathway [J]. EMBO J. 1997. 16, 3797-3804
32. Price, M. A. CKI, there's more than one: casein kinase I family members in Wnt and Hedgehog signaling [J]. Genes Dev. 2006. 20, 399-410
33. Tamai, K. et al. A mechanism for Wnt coreceptor activation [J]. Mol. Cell 2004. 13, 149-156
34. Davidson, G. et al. Casein kinase 1 gamma couples Wnt receptor activation to cytoplasmic signal transduction [J]. Nature 2005. 438, 867-872
35. Zeng, X. et al. A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation [J]. Nature 2005. 438, 873-877
36. Mao, J. et al. Low-density lipoprotein receptor-related protein-5 binds to Axin and regulates the canonical Wnt signaling pathway [J]. Mol. Cell 2001. 7, 801-809
37. Cselenyi, C. S. et al. LRP6 transduces a canonical Wnt signal independently of Axin degradation by inhibiting GSK3's phosphorylation of beta-catenin [J]. Proc. Natl. Acad. Sci. U. S. A 2008. 105, 8032-8037
38. Cliffe, A., Hamada, F. & Bienz, M. A role of Dishevelled in relocating Axin to the plasma membrane during wingless signaling [J]. Curr. Biol. 2003. 13, 960-966
39. Umbhauer, M. et al. The C-terminal cytoplasmic Lys-thr-X-X-X-Trp motif in frizzled receptors mediates Wnt/beta-catenin signalling [J]. EMBO J. 2000. 19, 4944-4954
40. Wong, H. C. et al. Direct binding of the PDZ domain of Dishevelled to a conserved internal sequence in the C-terminal region of Frizzled [J]. Mol. Cell 2003. 12, 1251-1260
41. Yanagawa, S., van, L. F., Wodarz, A., Klingensmith, J. & Nusse, R. The dishevelled protein is modified by wingless signaling in Drosophila [J]. Genes Dev. 1995. 9, 1087-1097
42. Gonzalez-Sancho, J. M., Brennan, K. R., Castelo-Soccio, L. A. & Brown, A. M. Wnt proteins induce dishevelled phosphorylation via an LRP5/6- independent mechanism, irrespective of their ability to stabilize beta-catenin [J]. Mol. Cell Biol. 2004. 24, 4757-4768
43. Swiatek, W. et al. Regulation of casein kinase I epsilon activity by Wnt signaling [J]. J. Biol. Chem. 2004. 279, 13011-13017
44. Ossipova, O., Dhawan, S., Sokol, S. & Green, J. B. Distinct PAR-1 proteins function in different branches of Wnt signaling during vertebrate development [J]. Dev. Cell 2005. 8, 829-841
45. Cong, F., Schweizer, L. & Varmus, H. Casein kinase Iepsilon modulates the signaling specificities of dishevelled [J]. Mol. Cell Biol. 2004. 24, 2000-2011
46. Capelluto, D. G. et al. The DIX domain targets dishevelled to actin stress fibres and vesicular membranes [J]. Nature 2002. 419, 726-729
47. Liu, T. et al. G protein signaling from activated rat frizzled-1 to the beta-catenin-Lef-Tcf pathway [J]. Science 2001. 292, 1718-1722

48. Malbon, C. C. Frizzleds: new members of the superfamily of G-protein-coupled receptors [J]. Front Biosci. 2004. 9, 1048-1058
49. Katanaev, V. L., Ponzielli, R., Semeriva, M. & Tomlinson, A. Trimeric G protein-dependent frizzled signaling in Drosophila [J]. Cell 2005. 120, 111-122
50. Cadigan, K. M. Wnt signaling--20 years and counting [J]. Trends Genet. 2002. 18, 340-342
51. Bienz, M. & Clevers, H. Armadillo/beta-catenin signals in the nucleus--proof beyond a reasonable doubt? [J]. Nat. Cell Biol. 2003. 5, 179-182
52. Choi, H. J., Huber, A. H. & Weis, W. I. Thermodynamics of beta-catenin-ligand interactions: the roles of the N- and C-terminal tails in modulating binding affinity [J]. J. Biol. Chem. 2006. 281, 1027-1038
53. Xing, Y., Clements, W. K., Kimelman, D. & Xu, W. Crystal structure of a beta-catenin/axin complex suggests a mechanism for the beta-catenin destruction complex [J]. Genes Dev. 2003. 17, 2753-2764
54. Cong, F. & Varmus, H. Nuclear-cytoplasmic shuttling of Axin regulates subcellular localization of beta-catenin [J]. Proc. Natl. Acad. Sci. U. S. A 2004. 101, 2882-2887
55. Rosin-Arbesfeld, R., Townsley, F. & Bienz, M. The APC tumour suppressor has a nuclear export function [J]. Nature 2000. 406, 1009-1012
56. Stadeli, R., Hoffmans, R. & Basler, K. Transcription under the control of nuclear Arm/beta-catenin [J]. Curr. Biol. 2006. 16, R378-R385
57. van de, W. M. et al. Armadillo coactivates transcription driven by the product of the Drosophila segment polarity gene dTCF [J]. Cell 1997. 88, 789-799
58. Korinek, V. et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma [J]. Science 1997. 275, 1784-1787
59. Hoppler, S. & Kavanagh, C. L. Wnt signalling: variety at the core [J]. J. Cell Sci. 2007. 120, 385-393
60. Cavallo, R. A. et al. Drosophila Tcf and Groucho interact to repress Wingless signalling activity [J]. Nature 1998. 395, 604-608
61. Roose, J. et al. The Xenopus Wnt effector XTcf-3 interacts with Groucho-related transcriptional repressors [J]. Nature 1998. 395, 608-612
62. Kitagawa, H. et al. A regulatory circuit mediating convergence between Nurr1 transcriptional regulation and Wnt signaling [J]. Mol. Cell Biol. 2007. 27, 7486-7496
63. Daniels, D. L. & Weis, W. I. Beta-catenin directly displaces Groucho/TLE repressors from Tcf/Lef in Wnt-mediated transcription activation [J]. Nat. Struct. Mol. Biol. 2005. 12, 364-371
64. Sierra, J., Yoshida, T., Joazeiro, C. A. & Jones, K. A. The APC tumor suppressor counteracts beta-catenin activation and H3K4 methylation at Wnt target genes [J]. Genes Dev. 2006. 20, 586-600
65. Mosimann, C., Hausmann, G. & Basler, K. Parafibromin/Hyrax activates Wnt/Wg target gene transcription by direct association with beta-catenin/Armadillo [J]. Cell 2006. 125, 327-341
66. Stadeli, R. & Basler, K. Dissecting nuclear Wingless signalling: recruitment of the transcriptional co-activator Pygopus by a chain of adaptor proteins [J]. Mech. Dev. 2005. 122, 1171-1182
67. Thompson, B., Townsley, F., Rosin-Arbesfeld, R., Musisi, H. & Bienz, M. A new nuclear component of the Wnt signalling pathway [J]. Nat. Cell Biol. 2002. 4, 367-373
68. Hoffmans, R., Stadeli, R. & Basler, K. Pygopus and legless provide essential transcriptional coactivator functions to armadillo/beta-catenin [J]. Curr. Biol. 2005. 15, 1207-1211
69. Parker, D. S., Jemison, J. & Cadigan, K. M. Pygopus, a nuclear PHD-finger protein required for Wingless signaling in Drosophila [J]. Development 2002. 129, 2565-2576
70. Gan, X. Q. et al. Nuclear Dvl, c-Jun, beta-catenin, and TCF form a complex leading to stabilization of beta-catenin-TCF interaction [J]. J. Cell Biol. 2008. 180, 1087-1100
71. Firestein, R. et al. CDK8 is a colorectal cancer oncogene that regulates beta-catenin activity [J]. Nature 2008. 455, 547-551
72. Morris, E. J. et al. E2F1 represses beta-catenin transcription and is antagonized by both pRB and CDK8 [J]. Nature 2008. 455, 552-556

73. Chinnadurai, G. CtBP, an unconventional transcriptional corepressor in development and oncogenesis [J]. Mol. Cell 2002. 9, 213-224
74. Tago, K. et al. Inhibition of Wnt signaling by ICAT, a novel beta-catenin-interacting protein [J]. Genes Dev. 2000. 14, 1741-1749
75. Hoogeboom, D. et al. Interaction of FOXO with beta-catenin inhibits beta-catenin/T cell factor activity [J]. J. Biol. Chem. 2008. 283, 9224-9230
76. Takemaru, K. et al. Chibby, a nuclear beta-catenin-associated antagonist of the Wnt/Wingless pathway [J]. Nature 2003. 422, 905-909
77. Ito, K. et al. RUNX3 attenuates beta-catenin/T cell factors in intestinal tumorigenesis [J]. Cancer Cell 2008. 14, 226-237
78. Mulholland, D. J., Dedhar, S., Coetzee, G. A. & Nelson, C. C. Interaction of nuclear receptors with the Wnt/beta-catenin/Tcf signaling axis: Wnt you like to know? [J]. Endocr. Rev. 2005. 26, 898-915
79. Logan, C. Y. & Nusse, R. The Wnt signaling pathway in development and disease [J]. Annu. Rev. Cell Dev. Biol. 2004. 20, 781-810
80. Jho, E. H. et al. Wnt/beta-catenin/Tcf signaling induces the transcription of Axin2, a negative regulator of the signaling pathway [J]. Mol. Cell Biol. 2002. 22, 1172-1183
81. Weidinger, G., Thorpe, C. J., Wuennenberg-Stapleton, K., Ngai, J. & Moon, R. T. The Sp1-related transcription factors sp5 and sp5-like act downstream of Wnt/beta-catenin signaling in mesoderm and neuroectoderm patterning [J]. Curr. Biol. 2005. 15, 489-500
82. Wnt homepage. http://www.stanford.edu/~rnusse/wntwindow.html. 2009.
83. Gregorieff, A. & Clevers, H. Wnt signaling in the intestinal epithelium: from endoderm to cancer [J]. Genes Dev. 2005. 19, 877-890
84. Korinek, V. et al. Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4 [J]. Nat. Genet. 1998. 19, 379-383
85. Ireland, H. et al. Inducible Cre-mediated control of gene expression in the murine gastrointestinal tract: effect of loss of beta-catenin [J]. Gastroenterology 2004. 126, 1236-1246
86. Sansom, O. J. et al. Loss of Apc in vivo immediately perturbs Wnt signaling, differentiation, and migration [J]. Genes Dev. 2004. 18, 1385-1390
87. van de, W. M. et al. The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells [J]. Cell 2002. 111, 241-250
88. Alonso, L. & Fuchs, E. Stem cells in the skin: waste not, Wnt not [J]. Genes Dev. 2003. 17, 1189-1200
89. Huelsken, J., Vogel, R., Erdmann, B., Cotsarelis, G. & Birchmeier, W. beta-Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin [J]. Cell 2001. 105, 533-545
90. Zhou, P., Byrne, C., Jacobs, J. & Fuchs, E. Lymphoid enhancer factor 1 directs hair follicle patterning and epithelial cell fate [J]. Genes Dev. 1995. 9, 700-713
91. Reya, T. & Clevers, H. Wnt signalling in stem cells and cancer [J]. Nature 2005. 434, 843-850
92. Hartmann, C. A Wnt canon orchestrating osteoblastogenesis [J]. Trends Cell Biol. 2006. 16, 151-158
93. Kato, M. et al. Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in Lrp5, a Wnt coreceptor [J]. J. Cell Biol. 2002. 157, 303-314
94. Okamura, R. M. et al. Redundant regulation of T cell differentiation and TCRalpha gene expression by the transcription factors LEF-1 and TCF-1 [J]. Immunity. 1998. 8, 11-20
95. Kinzler, K. W. et al. Identification of FAP locus genes from chromosome 5q21 [J]. Science 1991. 253, 661-665
96. Kinzler, K. W. & Vogelstein, B. Lessons from hereditary colorectal cancer [J]. Cell 1996. 87, 159-170
97. He, T. C. et al. Identification of c-MYC as a target of the APC pathway [J]. Science 1998. 281, 1509-1512
98. Tetsu, O. & McCormick, F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells [J]. Nature 1999. 398, 422-426
99. Liu, W. et al. Mutations in AXIN2 cause colorectal cancer with defective mismatch repair by activating beta-

catenin/TCF signalling [J]. Nat. Genet. 2000. 26, 146-147
100. Morin, P. J. et al. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC [J]. Science 1997. 275, 1787-1790
101. Lammi, L. et al. Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer [J]. Am. J. Hum. Genet. 2004. 74, 1043-1050
102. The Jackson Laboratory. http://jaxmice.jax.org/strain/002020.html. 2009.
103. Su, L. K. et al. Multiple intestinal neoplasia caused by a mutation in the murine homolog of the APC gene [J]. Science 1992. 256, 668-670
104. Gat, U., DasGupta, R., Degenstein, L. & Fuchs, E. De Novo hair follicle morphogenesis and hair tumors in mice expressing a truncated beta-catenin in skin [J]. Cell 1998. 95, 605-614
105. Chan, E. F., Gat, U., McNiff, J. M. & Fuchs, E. A common human skin tumour is caused by activating mutations in beta-catenin [J]. Nat. Genet. 1999. 21, 410-413
106. Takeda, H. et al. Human sebaceous tumors harbor inactivating mutations in LEF1 [J]. Nat. Med. 2006. 12, 395-397
107. Jamieson, C. H. et al. Granulocyte-macrophage progenitors as candidate leukemic stem cells in blast-crisis CML [J]. N. Engl. J. Med. 2004. 351, 657-667
108. McWhirter, J. R. et al. Oncogenic homeodomain transcription factor E2A-Pbx1 activates a novel WNT gene in pre-B acute lymphoblastoid leukemia [J]. Proc. Natl. Acad. Sci. U. S. A 1999. 96, 11464-11469
109. Wilson, A. J., Arango, D., Mariadason, J. M., Heerdt, B. G. & Augenlicht, L. H. TR3/Nur77 in colon cancer cell apoptosis [J]. Cancer Res. 2003. 63, 5401-5407
110. Lei Na-zi et al. A feedback regulatory loop between methyltransferase PRMT1 and orphan receptor TR3 [J]. Nucleic Acids Res. 2009. 37, 832-848
111. Li, G. D. et al. Negative regulation of transcription coactivator p300 by orphan receptor TR3 [J]. Nucleic Acids Res. 2007. 35, 7348-7359
112. Zhao, B. X. et al. p53 mediates the negative regulation of MDM2 by orphan receptor TR3 [J]. EMBO J. 2006. 25, 5703-5715
113. Martens, C., Bilodeau, S., Maira, M., Gauthier, Y. & Drouin, J. Protein-protein interactions and transcriptional antagonism between the subfamily of NGFI-B/Nur77 orphan nuclear receptors and glucocorticoid receptor [J]. Mol. Endocrinol. 2005. 19, 885-897
114. Rui, Y. et al. Axin stimulates p53 functions by activation of HIPK2 kinase through multimeric complex formation [J]. EMBO J. 2004. 23, 4583-4594
115. Liu, W. et al. Axin is a scaffold protein in TGF-beta signaling that promotes degradation of Smad7 by Arkadia [J]. EMBO J. 2006. 25, 1646-1658
116. Pinto, D., Robine, S., Jaisser, F., El Marjou, F. E. & Louvard, D. Regulatory sequences of the mouse villin gene that efficiently drive transgenic expression in immature and differentiated epithelial cells of small and large intestines [J]. J. Biol. Chem. 1999. 274, 6476-6482
117. Zhan, Y. et al. Cytosporone B is an agonist for nuclear orphan receptor Nur77 [J]. Nat. Chem. Biol. 2008. 4, 548-556
118. Kodama, S., Ikeda, S., Asahara, T., Kishida, M. & Kikuchi, A. Axin directly interacts with plakoglobin and regulates its stability [J]. J. Biol. Chem. 1999. 274, 27682-27688
119. Lepourcelet, M. et al. Small-molecule antagonists of the oncogenic Tcf/beta-catenin protein complex [J]. Cancer Cell 2004. 5, 91-102
120. Eklof, S. K., Fridman, S. G. & Weis, W. I. Molecular mechanisms of beta-catenin recognition by adenomatous polyposis coli revealed by the structure of an APC-beta-catenin complex [J]. EMBO J. 2001. 20, 6203-6212