Pathol. Oncol. Res. (2018) 24:245–250
DOI 10.1007/s12253-017-0243-1

ORIGINAL ARTICLE

Role of MAML1 and MEIS1 in Esophageal Squamous Cell Carcinoma Depth of Invasion

Mohammad Reza Abbaszadegan[1,2] · **Meysam Moghbeli**[3]

Received: 1 December 2016 / Accepted: 26 April 2017 / Published online: 1 May 2017
© Arányi Lajos Foundation 2017

Abstract Homeobox (HOX) transcription factors and NOTCH signaling pathway are critical regulators of stem cell functions, cell fate in development and homeostasis of gastrointestinal tissues. In the present study, we analyzed cross talk between NOTCH pathway and HOX genes through assessment of probable correlation betweenMAML1 and MEIS1 as the main transcription factor of NOTCH pathway and enhancer of HOX transcriptional machinery, respectively in esophageal squamous cell carcinoma (ESCC) patients. Fifty one ESCC cases were enrolled to assess the levels of Meis1 and Maml1 mRNA expression using real-time polymerase chain reaction (PCR). Only 3 out of 51 (5.9%) cases had MEIS1/MAML1 under expression and 2/51 (3.9%) cases had MEIS1/MAML1over expression. Nine out of 51 samples (17.6%) have shown MEIS1 under expression and MAML1 over expression. There was a significant correlation between MAML1and MEIS1mRNA expressions ($p \leq 0.05$). There were significant correlations between MEIS1 under/MAML1 over expressed cases and tumor location ($p = 0.05$), tumor depth of invasion ($p = 0.011$), and sex ($p = 0.04$). Our results showed that MEIS1 may have a negative role in regulation of MAML1expression during the ESCC progression.

✉ Meysam Moghbeli
m.moghbeli@nkums.ac.ir; Meysam_moghbeli@yahoo.com

[1] Division of Human Genetics, Immunology Research Center, Avicenna Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[2] Medical Genetics Research Center, Medical School, Mashhad University of Medical Sciences, Mashhad, Iran

[3] North Khorasan University of Medical Sciences, Bojnurd, Iran

Keywords NOTCH signaling pathway · HOX · mRNA expression · Transcription factor · Self renewal

Introduction

Esophageal cancer is the eighth leading cause of cancer related deaths in the world [1]. Apart from the new progresses in therapeutic modalities, ESCC patients have poor prognosis due to chemo radio therapeutic resistance. Different signaling pathways such as WNT and NOTCH are involved in ESCC progression and metastasis and there are complicated interactions between these pathways [2–8]. Notch is a cell–cell contact pathway including a family of transmembrane receptors (Notch1–Notch4) [9]. NOTCH pathway is activated by neighboring cell surface ligands leading to release the intracellular domain of Notch (ICN) into the cytoplasm. Then, ICN translocates to the nucleus and binds to the CSL family of DNA-binding transcription factors (CBF1/RBP-J) to activate this complex by substitution of transcriptional co-repressors, including CIR [10], SMRT/N-CoR [11], and KyoT2 [12], and recruitment of co-activators, including CBP/p300 [13], and mastermind-like proteins (MAML) [14, 15]. MAML family consists of MAML1–3 in humans which are able to bind with all four NOTCH receptors (ICN1–4) [16–18]. Multiprotein complex comprising of MAML1, CSL, and ICN activates transcription of Notch target genes following the stimulation of Notch receptors [19]. CSL acts as a suppressor in the absence of ICN, which recruits the SMRT (co-repressor) to inhibit the NOTCH target genes [10, 13]. MAML1 recruits Histone Acetyl Transferase (HAT) p300 to form an active transcriptional chromatin via Histone acetylation in H3 and H4 [20]. Homeobox (HOX) proteins are a family of transcription factors with a DNA binding homeodomain consisting of 60 conserved amino acids. This family is also involved in cell

fate and self-renewal and associated with MEIS and PBX as the main TALE homeodomain proteins [21, 22]. Regarding the inevitable role of homeobox genes in development and cell fate, every deregulation leads to the congenital diseases and cancer [23]. TALE/HOX complex recruits transcriptional co-repressor or coactivators to the promoter sequence of target genes [24, 25]. It has been shown that, Wnt and NOTCH signaling pathways have complicated association together (Fig. 1). GSK-3 as an important cytosolic mediator in Wnt pathway simplifies the expression of HOX target genes [26]. HOXA5, acts as a negative regulator of NOTCH pathway through the down regulation of HEY2 as one of the main NOTCH target genes [27]. The MEIS1 is an activator for the HOX members such as HOXA9, HOXA7 [28]. In a positive feedback, HOXA9 up regulates the Meis1 indirectly through the other mediators such as Creb1 and Pknox1 [29, 30]. Therefore, in the present study we assessed the probable similar correlation between MAML1 and MEIS1 to define a new correlation through such markers between the HOX and NOTCH signaling pathway for the first time in ESCC patients.

Materials and Methods

Tissue Samples

Fifty one ESCC patients were enrolled in the present study based on a specific criterion in which the cases should not have received any chemo radio therapeutic treatment before the tumor resection. Moreover, all the samples were examined histopathologically to ensure the presence of at least 70% of tumor cells. All the patients were gathered from Qaem and Emam Reza hospitals of Mashhad University of Medical Sciences from 2010 to 2015. Freshly resected tumors were transferred to the RNA later solution (Qiagen, Hilden, Germany) and stored at −20 C until the mRNA extraction. All the patients have filled the consent forms which were approved by the ethic committee of Mashhad University of Medical Sciences.

RNA Extraction, cDNA Synthesis, and Quantitative RT-PCR

RNA extraction from the normal and tumor tissues was done using the RNAeasy Mini kit (Qiagen, Germany). Then, cDNA synthesis was also performed by the First-Strand Synthesis kit (Fermentas, Lithuania). Comparative relative Real Time PCR (SYBR Green,AMPLIQON, Denmark) was used in Stratagene Mx-3000P real-time thermocycler (Stratagene, La Jolla, CA) to assess the levels of Maml1 and Meis1 mRNA (primer sequences and their thermal profiles are mentioned in our recent studies [31, 32]). cDNA was used in 100 ng/μl concentration. All the tests were normalized by the Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as a normalizer [31, 32].

Statistical Analysis

SPSS 16.0 (SPSS, Chicago, IL) software was used for the statistical analysis, to assess the probable correlation between the MAML1 and MEIS1 expression by Spearman's q and Pearson v-squared. Moreover, ANOVA and t-test ($p < 0.05$), were used to evaluate the probable correlations between the MEIS1/MAML1 mRNA expression and clinicopathological features of tumors.

Results

Study Population

Fifty one ESCC patients involving the 22 (43.1%) females and 29 (56.9%) males were enrolled in the present study. The general mean age was 62.20 ± 12.17, ranging from 30 to 83 years. Females were younger than the males (57.55 ± 2.85 vs.

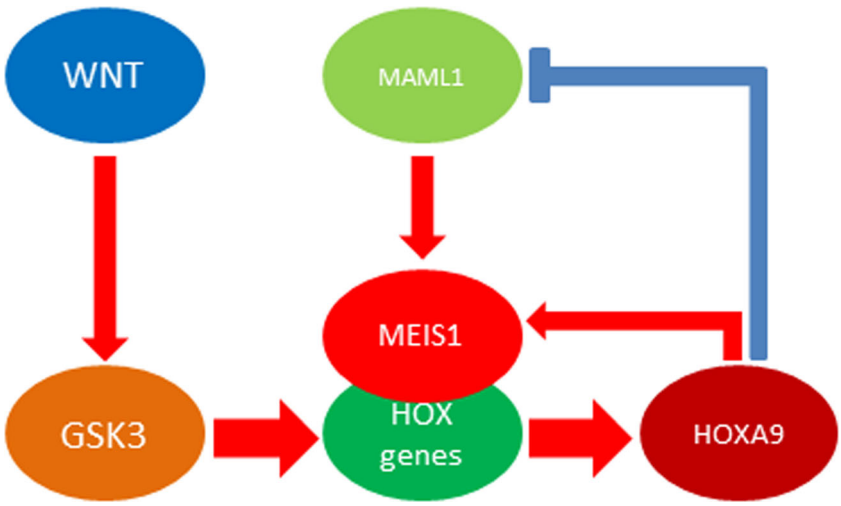

Fig. 1 MEIS1 acts as a mediator for the WNT and NOTCH crosstalk

65.72 ± 1.86 years). Mean size of tumors was 4.24 ± 1.91 cm, ranging from 1.5 to 12 cm. Majority of resected tumors were moderately differentiated (32/51, 62.7%), located in middle esophagus (28/51, 54.9%), metastatic lymph node (27/51, 52.9%), I/II stages of tumor (30/51, 58.8%), and T3 tumor depth of invasion (43/51, 84%). All the Clinicopathological features of patients are summarized in (Table 1).

Levels of MEIS1/MAML1 mRNA Expression in ESCC Patients

We have recently assessed the levels of MEIS1 and Maml1 mRNA expressions in ESCC patients in separate studies [6, 33]. In present study we performed a correlational study to find a probable interaction between such markers in Iranian ESCC patients. Only 3 out of 51 (5.9%) cases had MEIS1/MAML1 under expression and 2/51 (3.9%) cases had MEIS1/MAML1over expression. Nine out of 51 samples (17.6%) have shown MEIS1 under expression and MAML1 over expression. However, there was not any sample with MEIS1 over and MAML1 under expression. Moreover, thirteen out of 51 (25.5%) were normal for the expression of both of these markers. There was a significant correlation between MEIS1/MAML1 mRNA expressions in which, mean fold of MAML1 expression in MEIS1 under expressed cases was significantly higher than that in the MEIS1 over expressed cases (1.95 ± 0.87 vs. 1.54 ± 0.36, fold changes) ($p \leq 0.05$). Scatter plot represents the fold changes for the MAML1 and MEIS1 (Fig. 2).

Clinicopathological Features and MEIS1/MAML1 mRNA Expression

There was a significant correlation between MEIS1 under/MAML1 over expressed cases and tumor location in which most of such cases were located in middle esophagus (8/9, 88.9%) ($p = 0.05$). There was also a significant correlation between MEIS1 under/MAML1 over expressed cases and tumor depth of invasion, majority of cases had T3 depth of invasion (8/9, 88.9%) ($p = 0.011$). In the case of sex, levels of MEIS1 mRNA expression in males with MEIS1 under/MAML1 over expression were significantly lower than that in the females (−3.35 ± 0.57 vs. -2.60 ± 0.18, fold changes) ($p = 0.04$). Majority of MEIS1 under/MAML1 over expressed

Table 1 Correlation between level of MEIS1/MAML1 mRNA expression and clinicopathological features of ESCC patients

	Total	MAML1 over expression	MEIS1 Under expression	MAML1/ MEIS1 over expression	MAML1/ MEIS1 under expression	MAML1 over /MEIS1 under expression	*P- Value*
Patients	51	12 (23.5%)	8 (15.7%)	2 (3.9%)	3 (5.9%)	9 (17.6%)	
Mean age (mean ± SD)	62.20 ± 12.17	66.08 ± 3.10	58.12 ± 4.11	60.5 ± 2.5	63.33 ± 13.7	58.11 ± 2.79	
Size (mean ± SD)	4.24 ± 1.91	3.88 ± 0.34	5.19 ± 1.04	3.00 ± 1.50	5.17 ± 1.01	3.89 ± 0.64	
Sex							**0.040**
Male	29 (56.9%)	11 (91.7%)	1 (12.5%)	1 (50%)	2 (66.7%)	4 (44.4%)	
Female	22 (43.1%)	1 (8.3%)	7 (87.5%)	1 (50%)	1 (33.3%)	5 (55.6%)	
Location							**0.050**
Lower	23 (45.1%)	8 (66.7%)	3 (37.5%)	1 (50%)	3 (100%)	1 (11.1%)	
Middle	28 (54.9%)	4 (33.3%)	5 (62.5%)	1 (50%)	-	8 (88.9%)	
Grade							0.852
P.D	10 (19.6%)	3 (25%)	2 (25%)	1 (50%)	-	2 (22.2%)	
M.D	32 (62.8%)	7 (58.3%)	4 (50%)	1 (50%)	3 (100%)	5 (55.6%)	
W.D	9 (17.6%)	2 (16.7%)	2 (25%)	-	-	2 (22.2%)	
Lymph node							0.697
Yes	24 (47.1%)	7 (58.3%)	4 (50%)	-	1 (33.3%)	4 (44.4%)	
No	27 (52.9%)	5 (41.7%)	4 (50%)	2 (100%)	2 (66.7%)	5 (55.6%)	
Stage							0.786
I/II	30 (58.8%)	6 (50%)	4 (50%)	2 (100%)	2 (66.7%)	6 (66.7%)	
III/IV	21 (41.2%)	6 (50%)	4 (50%)	-	1 (33.3%)	3 (33.3%)	
Depth of tumor invasion (T)							**0.011**
T1	1 (2%)	-	-	1 (50%)	-	-	
T2	7 (13.7%)	1 (8.3%)	1 (12.5%)	-	1 (33.3%)	1 (11.1%)	
T3	43 (84.3%)	11 (91.7%)	7 (87.5%)	1 (50%)	2 (66.7%)	8 (88.9%)	

Bold values indicate significant correlation between mRNA expression and clinicopathological features

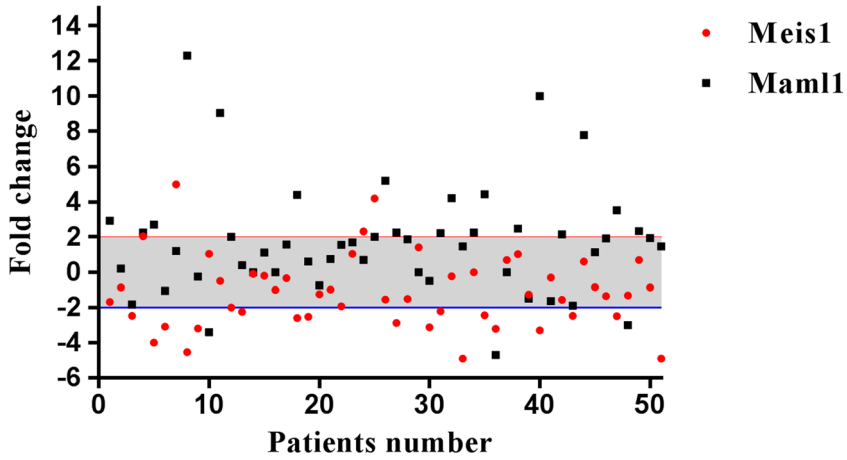

Fig. 2 Scatter plot represents a descriptive analysis of relative gene expression of MEIS1 and MAML1 in ESCC patients. The thresholds for the over- and under expressed cases are shown by the red and blue lines, respectively. The gray area mentions to the cases with normal levels of MAML1 and MEIS1 mRNA expression

cases were moderately differentiated (5/9, 55.6%), tumor stages of I/II (6/9, 66.7%), and had not any lymph node metastasis (5/9, 55.6%). All of the cases with over expression in both of these markers had not any lymph node metastasis and were in tumor stages of I/II. Moreover, all of the samples with under expression in both of such markers were moderately differentiated. There was not any significant correlation in tumor size and age of patients. The youngest patients were MEIS1 over expressed and oldest were MAML1 under expressed cases with mean ages of (55.5 ± 6.5, years) and (66.5 ± 2.5, years), respectively. In the case of tumor size, the biggest tumors were the MEIS1 under expressed cases and the smallest ones were the cases with over expression in both of these markers (5.19 ± 1.04 vs. 3.00 ± 1.5, cm). In both of such markers the levels of mRNA expressions in males are higher than that in the females. MAML1 had highest levels of expression in poorly differentiated cases (2.48 ± 0.94, fold changes), whereas MEIS1 had the highest expression in well differentiated cases (−0.9 ± 0.88, fold changes). In the case of tumor location also there was different patterns of expression between such markers, in which MEIS1 had highest levels of mRNA expression in the lower esophagus (−0.83 ± 0.31, fold changes) and MAML1 had the highest ratio of expression in the middle esophagus (1.93 ± 0.67, fold changes). The cases with T2 depth of invasion had higher levels of MEIS1 and lower levels of MAML1 mRNA expression (−0.587 ± 0.99 and 1.57 ± 1.37, fold changes) respectively, in comparison with the levels of mRNA expression in tumors with T3 depth of invasion. In the case of lymph node involvement, there was not any difference in levels of MEIS1 expression between cases with and without lymph node metastasis. Metastatic cases have shown higher levels of MAML1 mRNA expression in comparison with the cases without any lymph node metastasis (2.02 ± 0.65 vs. 1.37 ± 0.60, fold changes). Data have shown that, there is a reverse correlation between tumor size and levels of MEIS1/MAML1 mRNA expressions, in which bigger tumors had lower levels of mRNA expressions in such markers.

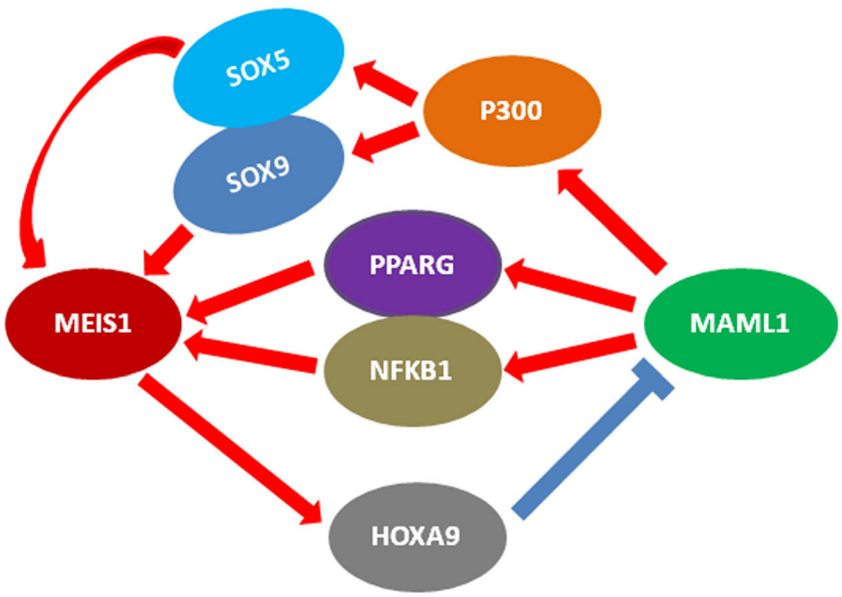

Fig. 3 Probable crosstalk between HOX and NOTCH pathways through the MEIS1 and MAML1, respectively

Discussion

A significant inverse correlation between MAML1 and MEIS1 showed a probable negative interaction between such markers. HOX/MEIS are involved in tumorigenesis through different processes such as cell cycle control, chromatin binding, apoptosis, and self-renewal [34–36]. In present study, we assessed the probable correlation between MEIS1 and MAML1 in ESCC patients to clarify a relationship between HOX and NOTCH pathways. Although, It has been shown that MEIS1functions as an oncogene by maintaining the hematopoietic cells in a dedifferentiated state [37–39], Meis1 under expression in ESCC patients refers to the role of this marker in apoptosis. There are two binding sites for the MEIS1/HOXA9 in promoter sequence of MAML1, referring to the probable negative role of this complex in MAML1 expression. Moreover, the MEIS1 also exerts its negative role on the MAML1 expression through the Numb, in which there is a binding site in the promoter sequence of Numb as the main NOTCH signaling inhibitor resulting to the down regulation of MAML1expression [6]. On the other hand, HOX family down regulates some of the NOTCH target genes such as HEY2 via the HOXA5. However this correlation is independent from MEIS1. Despite the negative role of MEIS1 on the MAML1 expression, it seems that the MAML1 up regulates the MEIS1 through some mediators such as NFKB1 and PPARG. Both of these mediators have binding sites in promoter sequence of MEIS1relying the probable role of such factors in MEIS1expression. Moreover, MAML1up regulates the MEIS1through the P300 as a mediator for activation of SOX9 and SOX5 which are the main activators for MEIS1expression (Fig. 3). It was shown that the tumors with MEIS1under and MAML1over expressions (8/9, 88.9%) have invaded significantly to the adventitia ($p = 0.011$). However, most of such cases had tumor stages of I/II, introducing this correlation as an efficient prognostic panel of markers in ESCC patients. Although such cases had more invasion ability to progress to the adventitia, there wasn't any significant correlation between lymph node metastasis and MEIS1under/MAML1over expression in ESCC patients. Previously we have shown that there is a correlation between MEIS1and WNT pathway in which, GSK3 functions as a mediator between MEIS1and MSI1 [4]. Msi1 targets the DKK3 as a WNT signaling inhibitor. MEIS1 also triggers the apoptosis through down regulation of anti-apoptotic factors such as XIAP [40] and PARP [41] and up regulates the pro-apoptotic factors such as cytochrome *c* [42] and CAS [43].

In conclusion, there is a probable negative feedback of MEIS1 on the MAML1 expression. Therefore, although there was a significant correlation between MEIS1/MAML1 expression and T3 depth of invasion, it seems that a panel of MEIS1and MAML1markers cannot be an efficient way in targeted therapy in ESCC patients.

Acknowledgements This work was supported by a grant from the Vice Chancellor for Research at Mashhad University of Medical Sciences, No. 921202.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Funding This work was supported by a grant from the Vice Chancellor for Research at Mashhad University of Medical Sciences, No. 921202.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61(2):69–90. doi:10.3322/caac.20107
2. Moghbeli M, Abbaszadegan MR, Farshchian M, Montazer M, Raeisossadati R, Abdollahi A, Forghanifard MM (2013) Association of PYGO2 and EGFR in esophageal squamous cell carcinoma. Med Oncol 30(2):516
3. Moghbeli M, Abbaszadegan MR, Golmakani E, Forghanifard MM (2016) Correlation of Wnt and NOTCH pathways in esophageal squamous cell carcinoma. J Cell Commun Signal 10(2):129–135
4. Moghbeli M, Forghanifard MM, Sadrizadeh A, Mozaffari HM, Golmakani E, Abbaszadegan MR (2015) Role of Msi1 and MAML1 in regulation of notch signaling pathway in patients with esophageal squamous cell carcinoma. J Gastrointest Cancer 46(4):365–369
5. Moghbeli M, Moghbeli F, Forghanifard MM, Garayali A, Abbaszadegan MR (2013) Cancer stem cell markers in esophageal cancer. American Journal of Cancer Science 2(1):37–50
6. Moghbeli M, Rad A, Farshchian M, Taghehchian N, Gholamin M, Abbaszadegan MR (2016) Correlation between Meis1 and Msi1 in esophageal squamous cell carcinoma. J Gastrointest Cancer 47(3):273–277
7. Moghbeli M, Sadrizadeh A, Forghanifard MM, Mozaffari HM, Golmakani E, Abbaszadegan MR (2016) Role of Msi1 and PYGO2 in esophageal squamous cell carcinoma depth of invasion. J Cell Commun Signal 10(1):49–53
8. Taleb S, Abbaszadegan MR, Moghbeli M, Roudbari NH, Forghanifard MM (2014) HES1 as an independent prognostic marker in esophageal squamous cell carcinoma. J Gastrointest Cancer 45(4):466–471
9. Artavanis-Tsakonas S, Rand MD, Lake RJ (1999) Notch signaling: cell fate control and signal integration in development. Science 284(5415):770–776
10. Hsieh JJ, Zhou S, Chen L, Young DB, Hayward SD (1999) CIR, a corepressor linking the DNA binding factor CBF1 to the histone deacetylase complex. Proc Natl Acad Sci U S A 96(1):23–28
11. Kao HY, Ordentlich P, Koyano-Nakagawa N, Tang Z, Downes M, Kintner CR, Evans RM, Kadesch T (1998) A histone deacetylase corepressor complex regulates the notch signal transduction pathway. Genes Dev 12(15):2269–2277
12. Taniguchi Y, Furukawa T, Tun T, Han H, Honjo T (1998) LIM protein KyoT2 negatively regulates transcription by association

with the RBP-J DNA-binding protein. Mol Cell Biol 18(1):644–654
13. Oswald F, Tauber B, Dobner T, Bourteele S, Kostezka U, Adler G, Liptay S, Schmid RM (2001) p300 acts as a transcriptional coactivator for mammalian notch-1. Mol Cell Biol 21(22):7761–7774. doi:10.1128/MCB.21.22.7761-7774.2001
14. Kurooka H, Honjo T (2000) Functional interaction between the mouse notch1 intracellular region and histone acetyltransferases PCAF and GCN5. J Biol Chem 275(22):17211–17220. doi:10.1074/jbc.M000909200
15. Wu L, Sun T, Kobayashi K, Gao P, Griffin JD (2002) Identification of a family of mastermind-like transcriptional coactivators for mammalian notch receptors. Mol Cell Biol 22(21):7688–7700
16. Kitagawa M, Oyama T, Kawashima T, Yedvobnick B, Kumar A, Matsuno K, Harigaya K (2001) A human protein with sequence similarity to drosophila mastermind coordinates the nuclear form of notch and a CSL protein to build a transcriptional activator complex on target promoters. Mol Cell Biol 21(13):4337–4346. doi:10.1128/MCB.21.13.4337-4346.2001
17. Lin SE, Oyama T, Nagase T, Harigaya K, Kitagawa M (2002) Identification of new human mastermind proteins defines a family that consists of positive regulators for notch signaling. J Biol Chem 277(52):50612–50620. doi:10.1074/jbc.M209529200
18. Wu L, Aster JC, Blacklow SC, Lake R, Artavanis-Tsakonas S, Griffin JD (2000) MAML1, a human homologue of drosophila mastermind, is a transcriptional co-activator for NOTCH receptors. Nat Genet 26(4):484–489. doi:10.1038/82644
19. Jeffries S, Robbins DJ, Capobianco AJ (2002) Characterization of a high-molecular-weight notch complex in the nucleus of notch(ic)-transformed RKE cells and in a human T-cell leukemia cell line. Mol Cell Biol 22(11):3927–3941
20. Saint Just Ribeiro M, Hansson ML, Wallberg AE (2007) A proline repeat domain in the notch co-activator MAML1 is important for the p300-mediated acetylation of MAML1. Biochem J 404(2):289–298. doi:10.1042/BJ20061900
21. Owens BM, Hawley RG (2002) HOX and non-HOX homeobox genes in leukemic hematopoiesis. Stem Cells 20(5):364–379
22. Sitwala KV, Dandekar MN, Hess JL (2008) HOX proteins and leukemia. Int J Clin Exp Pathol 1(6):461–474
23. Cillo C, Cantile M, Faiella A, Boncinelli E (2001) Homeobox genes in normal and malignant cells. J Cell Physiol 188(2):161–169
24. Goh SL, Looi Y, Shen H, Fang J, Bodner C, Houle M, Ng AC, Screaton RA, Featherstone M (2009) Transcriptional activation by MEIS1A in response to protein kinase a signaling requires the transducers of regulated CREB family of CREB co-activators. J Biol Chem 284(28):18904–18912
25. Huang H, Rastegar M, Bodner C, Goh SL, Rambaldi I, Featherstone M (2005) MEIS C termini harbor transcriptional activation domains that respond to cell signaling. J Biol Chem 280(11):10119–10127
26. Wang Z, Iwasaki M, Ficara F, Lin C, Matheny C, Wong SH, Smith KS, Cleary ML (2010) GSK-3 promotes conditional association of CREB and its coactivators with MEIS1 to facilitate HOX-mediated transcription and oncogenesis. Cancer Cell 17(6):597–608
27. Boucherat O, Chakir J, Jeannotte L (2012) The loss of Hoxa5 function promotes notch-dependent goblet cell metaplasia in lung airways. Biol Open 1(7):677–691
28. Chariot A, Gielen J, Merville MP, Bours V (1999) The homeodomain-containing proteins: an update on their interacting partners. Biochem Pharmacol 58(12):1851–1857
29. Esparza SD, Chang J, Shankar DB, Zhang B, Nelson SF, Sakamoto KM (2008) CREB regulates Meis1 expression in normal and malignant hematopoietic cells. Leukemia 22(3):665–667. doi:10.1038/sj.leu.2404933
30. Ferretti E, Villaescusa JC, Di Rosa P, Fernandez-Diaz LC, Longobardi E, Mazzieri R, Miccio A, Micali N, Selleri L, Ferrari G, Blasi F (2006) Hypomorphic mutation of the TALE gene Prep1 (pKnox1) causes a major reduction of Pbx and Meis proteins and a pleiotropic embryonic phenotype. Mol Cell Biol 26(15):5650–5662. doi:10.1128/MCB.00313-06
31. Moghbeli M, Maleknejad M, Arabi A, Abbaszadegan MR (2012) Mutational analysis of uroporphyrinogen III cosynthase gene in Iranian families with congenital erythropoietic porphyria. Mol Biol Rep 39(6):6731–6735
32. Forghanifard MM, Moghbeli M, Raeisossadati R, Tavassoli A, Mallak AJ, Boroumand-Noughabi S, Abbaszadegan MR (2013) Role of SALL4 in the progression and metastasis of colorectal cancer. J Biomed Sci 20:6
33. Forghanifard MM, Moaven O, Farshchian M, Montazer M, Raeisossadati R, Abdollahi A, Moghbeli M, Nejadsattari T, Parivar K, Abbaszadegan MR (2012) Expression analysis elucidates the roles of MAML1 and Twist1 in esophageal squamous cell carcinoma aggressiveness and metastasis. Ann Surg Oncol 19(3):743–749
34. Grier DG, Thompson A, Kwasniewska A, McGonigle GJ, Halliday HL, Lappin TR (2005) The pathophysiology of HOX genes and their role in cancer. J Pathol 205(2):154–171. doi:10.1002/path.1710
35. Wermuth PJ, Buchberg AM (2005) Meis1-mediated apoptosis is caspase dependent and can be suppressed by coexpression of HoxA9 in murine and human cell lines. Blood 105(3):1222–1230. doi:10.1182/blood-2004-03-0802
36. Yamashita T, Tazawa S, Yawei Z, Katayama H, Kato Y, Nishiwaki K, Yokohama Y, Ishikawa M (2006) Suppression of invasive characteristics by antisense introduction of overexpressed HOX genes in ovarian cancer cells. Int J Oncol 28(4):931–938
37. Argiropoulos B, Yung E, Humphries RK (2007) Unraveling the crucial roles of Meis1 in leukemogenesis and normal hematopoiesis. Genes Dev 21(22):2845–2849. doi:10.1101/gad.1619407
38. Calvo KR, Knoepfler PS, Sykes DB, Pasillas MP, Kamps MP (2001) Meis1a suppresses differentiation by G-CSF and promotes proliferation by SCF: potential mechanisms of cooperativity with Hoxa9 in myeloid leukemia. Proc Natl Acad Sci U S A 98(23):13120–13125. doi:10.1073/pnas.231115398
39. Kumar AR, Li Q, Hudson WA, Chen W, Sam T, Yao Q, Lund EA, Wu B, Kowal BJ, Kersey JH (2009) A role for MEIS1 in MLL-fusion gene leukemia. Blood 113(8):1756–1758. doi:10.1182/blood-2008-06-163287
40. Deveraux QL, Roy N, Stennicke HR, Van Arsdale T, Zhou Q, Srinivasula SM, Alnemri ES, Salvesen GS, Reed JC (1998) IAPs block apoptotic events induced by caspase-8 and cytochrome c by direct inhibition of distinct caspases. EMBO J 17(8):2215–2223. doi:10.1093/emboj/17.8.2215
41. Lindahl T, Satoh MS, Poirier GG, Klungland A (1995) Post-translational modification of poly(ADP-ribose) polymerase induced by DNA strand breaks. Trends Biochem Sci 20(10):405–411
42. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES, Wang X (1997) Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell 91(4):479–489
43. Brinkmann U, Brinkmann E, Gallo M, Pastan I (1995) Cloning and characterization of a cellular apoptosis susceptibility gene, the human homologue to the yeast chromosome segregation gene CSE1. Proc Natl Acad Sci U S A 92(22):10427–10431