Clin Oral Invest (2013) 17:2011–2015
DOI 10.1007/s00784-013-0920-8

ORIGINAL ARTICLE

High HIF-1α expression genotypes in oral lichen planus

Carlos Alberto de Carvalho Fraga · Lucas Rodrigues Alves · Luciano Marques-Silva · Adriana Alkmim de Sousa · Antonio Sérgio Barcala Jorge · Sabrina Ferreira de Jesus · Daniel Nogueira Vilela · Ugo Borges Pinheiro · Kimberly Marie Jones · Alfredo Maurício Batista de Paula · André Luiz Sena Guimarães

Received: 30 May 2012 / Accepted: 7 January 2013 / Published online: 19 January 2013

Abstract
Objective The aim of this study is to assess whether C1772T and G1790A hypoxia-inducible factor-1 (HIF-1)α polymorphisms are associated with risk of oral lichen planus (OLP).
Material and methods Restriction fragment length polymorphism analysis was used to investigate HIF-1α C1779T and G1790A polymorphisms in 32 OLP and 88 individuals without OLP.
Results The frequency of the CC, TT, GA, and AA genotypes was higher in patients with OLP. Notably, individuals carrying the C and A, and T and A haplotypes showed a significant association OLP risk.
Conclusions Our study demonstrated that the C1772T and G1790A polymorphisms of HIF-1α gene increased the risk of OLP. C1772T and G1790A polymorphisms of HIF-1α gene had differing patterns of allelic imbalance in the normal samples and subsequent chronic lesions. Further studies are necessary to elucidate the HIF-1α pathway in OLP, which would facilitate the development of novel therapeutic strategies for the prevention and treatment of OLP.
Clinical relevance These results, in conjunction with previous studies, suggest that HIF-1α may play important roles in the chronicity of oral mucosa lesions of OLP patients. Taken together, we suggest that HIF-1α polymorphisms enhance its target genes, thereby altering the microenvironment and supporting sequential release of inflammatory mediators or cellular events in OLP. It appears unlikely that inhibition of a single proinflammatory mediator will prove useful in clinical practice, but several ways to reprogram mediators engaged in a wide array of roles simultaneously are encouraging.

Keywords Hypoxia · Angiogenesis · Chronicity · Oral mucosa · Inflammation

C. A. de Carvalho Fraga · L. R. Alves · L. Marques-Silva · A. A. de Sousa · S. F. de Jesus · D. N. Vilela · U. B. Pinheiro · K. M. Jones · A. M. B. de Paula · A. L. S. Guimarães
Department of Dentistry, Universidade Estadual de Montes Claros, Montes Claros, Brazil

A. S. B. Jorge
Department of Medicine, Universidade Estadual de Montes Claros, Montes Claros, Brazil

A. L. S. Guimarães (✉)
Hospital Universitário Clemente de Faria, Avenida Cula Mangabeira, 562,
Montes Claros, Minas Gerais, Brazil 39400-000
e-mail: andreluizguimaraes@gmail.com

Introduction

The analysis of hypoxic and angiogenic-like proteins suggests that they might play a certain role in the pathogenesis of oral lichen planus (OLP). Hypoxic response is regulated by hypoxia-inducible factor-1 (HIF-1), which is a basic helix-loop-helix transcription factor composed of two subunits: HIF-1α and HIF-1β [1, 2]. HIF-1α translocates into the nucleus and heterodimerizes with HIF-1β. HIF-1 complex then binds to hypoxia response elements, which are present in the promoter or enhancer regions of HIF-1 target genes [3].

Thus, a proximity of HIF-1 complex and inflammatory mediators may directly take part in the etiopathology of autoimmune diseases [4, 5]. Overexpression of HIF-1α protein has been found to be involved in the pathogenesis of many inflammatory or autoimmune diseases including lupus nephritis [6], osteoarthritis [7], and rheumatoid arthritis [8]. HIF-1α overexpression can be regulated at a transcriptional level

[9, 10] and variation in HIF-1α production can be genetically determined.

Several studies have demonstrated that a base change of C to T at 1772 or G to A at 1790 in exon 12 of HIF-1α gene can increase the transcriptional activity [9, 10]. We previously reported that C1772T and G1790A HIF-1α polymorphisms increase HIF-1α protein expression in head and neck squamous cell carcinoma (HNSCC). T and A alleles have been observed to be associated with susceptibility to a number of diseases including oral [11], prostate [12], and lung cancers [13].

OLP is a chronic inflammatory oral disease, which has been reported to be associated to a cell-mediated immune process involving initiating egress of T lymphocytes at basal layer of oral mucosa [14, 15]. The diagnosis of OLP is usually achieved by clinical and histological examination [14]. Nevertheless, in classical lesions, it is possible to accomplish the diagnosis based solely on clinical appearance. Differential diagnosis includes lichenoid reactions to drugs/dental materials, leukoplakia, lupus erythematosus, and graft versus host disease in hematopoietic stem cell transplantation patients [14–16]. The etiology of the disease remains unclear, but several causative factors have been associated such as: anxiety, diabetes, autoimmune intestinal diseases, drugs, stress, hypertension, infections, dental materials, neoplasms, and genetic predisposition [16–28]. It has been demonstrated that overexpression of HIF-1α protein might play important roles in the chronicity of oral mucosa lesions of OLP patients [29]. However, to our knowledge, no study has associated C1772T and G1790A HIF-1α polymorphism, and OLP. Based on these data, the aim of this study is to assess whether C1772T and G1790A HIF-1α polymorphisms are associated with risk of OLP.

Material and methods

Ethical approval for this study was obtained from the relevant Institutional Review Board (UNIMONTES/IRB-1133/2008).

Study design and tissue specimens

This cross-sectional study was performed on archived tissue blocks from surgically resected specimens of OLP (n=32; male-to-female ratio=1:1.9; mean age=53.47±20.40 years). As a control group, 88 individuals without lichen planus were enrolled. Data related to patients and samples were obtained from the Department of Dentistry at the State University of Montes Claros, Minas Gerais, Brazil. All patients were from the same geographical area, but description of skin color was not used because, in Brazil, it is a poor predictor of genomic ancestry [30, 31]. The diagnoses of patients presenting OLP lesions were confirmed by clinical examination and histopathological evaluation [16].

DNA isolation and HIF-1α genotyping

DNA was isolated from ten 10 μm tissue sections from each tissue block of HNSCC specimens using the DNeasy Tissue kit (Qiagen, Chatsworth, CA) as described previously. Oral mucosal cell samples from healthy patients were collected during oral clinical examinations. The DNA extraction was carried out as described by Boom et al. [32] and modified as in Farias et al. [33].

HIF-1α (C1772T and G1790A) polymorphisms were assessed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). Polymerase chain reaction for HIF-1α was performed in a total volume of 25 μL containing approximately 100 ng genomic DNA as a template, 0.5 μL of each primer (20 pmol/μL), 2.5 μL dNTP mix (25 mM of each, Amresco, Ohio, CA, USA), 2.5 μL 10× PCR buffer, 1.25 μL magnesium chloride (50 mM), and 2.5 units of Platinum Taq DNA polymerase (Invitrogen Life Technologies, Carlsbad, CA, USA). DNA sequencing of each product was performed to confirm the PCR-RFLP genotyping. The conditions for the PCR assay were denaturation at 95 °C for 5 min followed by 35 cycles of denaturation at 95 °C for 1 min, annealing at 57.4 °C for 1 min and extension at 72 °C for 1 min, and a final extension at 72 °C for 10 min. The forward primer was 5′ AAG GTG TGG CCA TTG TAA AAA CTC 3′, and the reverse primer was 5′ CAG TGG TAG TGG TGG C 3′. This primer pair produced a fragment of 240 bp. The 240-bp PCR product of the HIF-1α gene was digested using the SsiI (Acil) restriction endonuclease (Fermentas Life Sciences) for the G1790A polymorphism. The substitution from a G to an A allele produces a single cut site to give two bands of 146 and 94 bp. For the C1772T polymorphism, the 240-bp PCR product of the HIF-1α gene was digested using the HphI restriction endonuclease (Fermentas Life Sciences). The substitution from a C to a T allele produces a single cut site to produce two bands, of 131 and 109 bp [9].

Electrophoresis

Digested fragments of the PCR products were analyzed on a 6.5 % polyacrylamide gel that was electrophoresed at 120 V at constant voltage for 1.5 h and stained with Safe DNA gel stain (Invitrogen). Electrophoresis results were estimated by comparing fragment sizes to a 100-bp ladder.

Statistical analysis

Frequency tests were selected for the statistical analysis of results, using the Chi-square and Fisher's exact statistical tests. All statistical analyses were performed with the

statistical software package SPSS®, version 13.0 for Windows®. p values <0.05 were considered significant.

Results

Sociodemographical, clinicopathologic, and HIF-1α polymorphisms characteristic of healthy and OLP patients

In OLP samples, of the total study population, 34.4 % of the patients were male. The most common anatomical site was the buccal mucosa (n=23) followed by the tongue border (n=04). Fifteen (46.9 %) and 19 (59.4 %) patients have tobacco and alcohol use, respectively. According to controls, 54 (61.4 %) of patients were female. Sixty-two (70.5 %) patients and 61 (69.3 %) of patients did not have tobacco and alcohol use, respectively.

Molecular data in controls and OLP samples

To determine whether the presence of either of two single nucleotide polymorphisms of the HIF-1α gene is associated with the development of OLP in the study population, 88 (controls) individuals without OLP were enrolled. The distribution of HIF-1α genotypes according to the presence of OLP is shown in Table 1. The frequency of the CC, TT, GA, and AA genotypes was higher in patients with OLP (Table 1). Table 2 shows multivariate comparisons between HIF-1α haplotypes and OLP. Notably, individuals carrying the C and A, and T and A haplotypes showed a significant association OLP risk.

Discussion

Although a background of genetic factors modulates the biological behavior of several diseases, even with the increasing number of studies in these fields, the clinical significance of these alterations in gene expression has not yet been established [20, 21, 33–35]. DNA polymorphisms have been appointed as a pivotal modulator of the biological behavior of inflammatory diseases [20, 21, 25–27]. OLP, like any analogous chronic inflammatory disease, is one of the most common dermatological diseases presenting in the oral cavity. However, the mechanisms by which this disease develops remain unknown [14–16, 36, 37].

HIF-1 is a well-studied transcription factor complex, which is a basic helix-loop-helix transcription factor composed of two subunits: HIF-1α and HIF-1β. HIF-1 is activated in hypoxic condition in mammalian cells, and it then regulates transcription of genes in angiogenesis, erythropoiesis, glycolysis, iron metabolism, and cell survival [38–40]. C1772T and G1790A polymorphism in exon 12 of the HIF-1α gene increase the transcriptional activity of this gene compared to the wild-type isoform, and the higher overexpression of HIF-1α protein is associated with presence of metastasis and decrease in survival of solid tumors [9, 13]. TT and AA genotypes increases HIF-1α protein with a consequent negative impact on survival in HNSCC patients [9].

To our knowledge, the present study is the first one that investigates the association between C1772 and G1790A polymorphisms of HIF-1α gene in OLP patients. We observed that CC, TT, GA, and AA genotypes were frequently higher in OLP samples when compared with controls. Higher expression of HIF-1α is associated with chronicity of oral mucosa lesions in OLP [29]. Moreover, increased expression of its target genes might modify metabolic reprogramming and angiogenesis in these lesions [41].

As an autoimmune disease with an inflammatory origin and chronic progression, OLP satisfies all the prerequisites of hypoxia at the base of the angiogenetic mechanism caused by the proliferating inflammatory elements [5, 16]. Angiogenesis is a fundamental process required for a number of physiological. It has been associated with pathogenesis of chronic

Table 1 Genotype and allele frequencies of the C1772T and G1790A polymorphisms of the HIF-1α gene in control and OLP patients

Gene Variant/genotype	Controls n(%)	Oral lichen planus n(%)	p value
C1772T			
CC	0 (0)	16 (50.0)	
CT	85 (96.6)	04 (12.5)	**<0.001**[a]
TT	03 (3.4)	12 (37.5)	
G1790A			
GG	81 (92.0)	02 (6.3)	
GA	07 (8.0)	26 (81.3)	**<0.001**[a]
AA	0 (0)	04 (12.5)	

[a] All values were calculated using the χ^2 test

In bold, statistically significant results

Table 2 HIF-1α haplotypes associated to risk of oral lichen planus evaluated by binary logistic regression

Variables	OR (95 % CI)			p value
	OR	Lower	Upper	
HIF-1α haplotypes				
C and G	Reference			
C and A	9.444	3.338	26.723	**<0.001**[a]
T and G	0.751	0.352	1.605	0.460
T and A	10.119	3.608	28.380	**<0.001**[a]

[a] All values were calculated using the χ^2 test

A significance level of $p \leq 0.05$ was used. *OR* odds ratio; *CI* confidence interval

In bold, statistically significant results

inflammatory pathologies and represents the base of the activity of OLP. Emerging evidence suggests that HIF-1α has important and independent effects on pathological angiogenesis. Hypoxic effect on the inflamed stromal area caused by an increase of the proliferating lymphocitary cellular mass has been associated with increase angiogenic factor in OLP samples [16, 26, 29, 42].

Several studies suggest that the increased expression of DNA methyltransferases is associated with a predisposition to aberrant DNA methylation and, consequently, a change in gene expression [43]. DNA methyltransferase 1 (DNMT1) protein hypermethylates genes associated with immunologically mediated diseases [44–47]. We previously observed in these OLP samples overexpression of DNMT1 protein levels [48]. Studies reveal the opposite roles of HIF-1α and DNMT1. While increases of HIF-1α protein expression results in enhanced apoptosis because of the activation of tumor suppressor p53, silencing of proapoptotic genes is the result of promoter methylation by DNMT1 induced via the MEK pathway. Moreover, HIF-1 has been found to bind specific sites on the promoter of the histone 3 lysine 9 demethylases (H3K9). Removal of H3K9 methyl marks looses chromatin compaction, exposing the DNA to instability, or abnormal transcription of otherwise silent genes [43].

These results, in conjunction with previous studies [29, 41–43], suggest that HIF-1α may play important roles in the chronicity of oral mucosa lesions of OLP patients. Taken together, we suggest that HIF-1α polymorphisms enhance its target genes, thereby altering the microenvironment and supporting sequential release of inflammatory mediators or cellular events in OLP. It appears unlikely that inhibition of a single proinflammatory mediator will prove useful in clinical practice, but several ways to reprogram mediators engaged in a wide array of roles simultaneously are encouraging [49].

Conclusion

In conclusion, our study demonstrated that the C1772T and G1790A polymorphisms of HIF-1α gene increased the risk of OLP. C1772T and G1790A polymorphisms of HIF-1α gene had differing patterns of allelic imbalance in the normal samples and subsequent chronic lesions. Further studies are necessary to elucidate the HIF-1α pathway in OLP, which would facilitate the development of novel therapeutic strategies for the prevention and treatment of OLP.

Acknowledgments This study was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico and the Fundação de Amparo a Pesquisa do Estado de Minas Gerais. Dr Guimarães is a research fellow of CNPq. Dr De Paula is a research fellow of FAPEMIG.

Conflict of interest No conflicts declared.

References

1. Maxwell PH, Pugh CW, Ratcliffe PJ (2001) Activation of the HIF pathway in cancer. Curr Opin Genet Dev 11:293–299
2. Wang GL, Jiang BH, Rue EA, Semenza GL (1995) Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O_2 tension. Proc Natl Acad Sci U S A 92:5510–5514
3. Wenger RH, Stiehl DP and Camenisch G (2005) Integration of oxygen signaling at the consensus HRE. Sci STKE 2005(306): re12
4. Hellwig-Burgel T, Stiehl DP, Wagner AE, Metzen E, Jelkmann W (2005) Review: hypoxia-inducible factor-1 (HIF-1): a novel transcription factor in immune reactions. J Interferon Cytokine Res 25:297–310
5. Haddad JJ, Harb HL (2005) Cytokines and the regulation of hypoxia-inducible factor (HIF)-1alpha. Int Immunopharmacol 5:461–483
6. Ma C, Wei J, Zhan F, Wang R, Fu K, Wan X et al (2012) Urinary hypoxia-inducible factor-1alpha levels are associated with histologic chronicity changes and renal function in patients with lupus nephritis. Yonsei Med J 53:587–92
7. Giatromanolaki A, Sivridis E, Maltezos E, Athanassou N, Papazoglou D, Gatter KC et al (2003) Upregulated hypoxia inducible factor-1alpha and -2alpha pathway in rheumatoid arthritis and osteoarthritis. Arthritis Res Ther 5:R193–201
8. Ha MK, Song YH, Jeong SJ, Lee HJ, Jung JH, Kim B et al (2011) Emodin inhibits proinflammatory responses and inactivates histone deacetylase 1 in hypoxic rheumatoid synoviocytes. Biol Pharm Bull 34:1432–7
9. Fraga CA, de Oliveira MV, de Oliveira ES, Barros LO, Santos FB, Gomez RS et al (2012) A high HIF-1alpha expression genotype is associated with poor prognosis of upper aerodigestive tract carcinoma patients. Oral Oncol 48:130–5
10. Tanimoto K, Yoshiga K, Eguchi H, Kaneyasu M, Ukon K, Kumazaki T et al (2003) Hypoxia-inducible factor-1alpha polymorphisms associated with enhanced transactivation capacity, implying clinical significance. Carcinogenesis 24:1779–1783
11. Munoz-Guerra MF, Fernandez-Contreras ME, Moreno AL, Martin ID, Herraez B, Gamallo C (2009) Polymorphisms in the hypoxia inducible factor 1-alpha and the impact on the prognosis of early stages of oral cancer. Ann Surg Oncol 16:2351–2358
12. Chau CH, Permenter MG, Steinberg SM, Retter AS, Dahut WL, Price DK et al (2005) Polymorphism in the hypoxia-inducible factor 1alpha gene may confer susceptibility to androgen-independent prostate cancer. Cancer Biol Ther 4:1222–1225
13. Putra AC, Tanimoto K, Arifin M, Hiyama K (2011) Hypoxia-inducible factor-1 alpha polymorphisms are associated with genetic aberrations in lung cancer. Respirology 16:796–802
14. Epstein JB, Wan LS, Gorsky M, Zhang L (2003) Oral lichen planus: progress in understanding its malignant potential and the implications for clinical management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96:32–37
15. Gonzalez-Moles MA, Scully C, Gil-Montoya JA (2008) Oral lichen planus: controversies surrounding malignant transformation. Oral Dis 14:229–243
16. Scully C, Carrozzo M (2008) Oral mucosal disease: lichen planus. Br J Oral Maxillofac Surg 46:15–21
17. Caetano FA, Beraldo FH, Hajj GN, Guimaraes AL, Jurgensen S, Wasilewska-Sampaio AP et al (2011) Amyloid-beta oligomers increase the localization of prion protein at the cell surface. JNeurochem 117:538–553

18. Gomes CC, Drummond SN, Guimaraes AL, Andrade CI, Mesquita RA, Gomez RS (2008) P21/ WAF1 and cyclin D1 variants and oral squamous cell carcinoma. J Oral Pathol Med 37:151–156
19. Gomez RS, Pimenta FJ, Guimaraes AL, Souza LN, Salomao UE, de Almeida HC et al (2004) Effect of bone marrow transplantation on the immunolocalization of p53, hMSH2, and hMLH1 proteins on oral mucosa. Oral Dis 10:207–211
20. Guimaraes AL, Correia-Silva JF, Diniz MG, Xavier GM, Horta MC, Gomez RS (2007) Investigation of functional gene polymorphisms: IL-1B, IL-6 and TNFA in benign migratory glossitis in Brazilian individuals. J Oral Pathol Med 36:533–537
21. Guimaraes AL, de Sa AR, Victoria JM, de FC-S, Gomez MV, Gomez RS (2006) Interleukin-1beta and serotonin transporter gene polymorphisms in burning mouth syndrome patients. J Pain 7:654–658
22. Guimaraes AL, Gomes CC, da Silva LM, Correia-Silva JF, Victoria JM, Gomez RS et al (2009) Association between oral HSV-1 and survival in allogeneic hematopoietic stem cell transplanted patients. Med Oral Patol Oral Cir Bucal 14:E62–E68
23. Guimaraes AL, Perdigao PF, Siqueira FM, Castro WH, Gomez RS (2003) Oral metastasis of breast carcinoma diagnosed by fine needle aspiration cytology. A case report. Acta Cytol 47:1074–1076
24. Marques-Silva L, Castro WH, Gomez EL, Guimaraes AL, Silva MS, Gomez RS (2007) The impact of dental surgery on HSV-1 reactivation in the oral mucosa of seropositive patients. J Oral Maxillofac Surg 65:2269–2272
25. Moreira PR, Guimaraes MM, Guimaraes AL, Diniz MG, Gomes CC, Brito JA et al (2009) Methylation of P16, P21, P27, RB1 and P53 genes in odontogenic keratocysts. J Oral Pathol Med 38:99–103
26. Perdigao PF, Guimaraes AL, Victoria JM, Xavier GM, Romano-Silva MA, Gomez RS (2007) Serotonin transporter gene polymorphism (5-HTTLPR) in patients with oral lichen planus. Arch Oral Biol 52:889–893
27. Victoria JM, Guimaraes AL, da Silva LM, Kalapothakis E, Gomez RS (2005) Polymerase chain reaction for identification of herpes simplex virus (HSV-1), cytomegalovirus (CMV) and human herpes virus-type 6 (HHV-6) in oral swabs. Microbiol Res 160:61–65
28. Xavier GM, de Sa AR, Guimaraes AL, da Silva TA, Gomez RS (2007) Investigation of functional gene polymorphisms interleukin-1beta, interleukin-6, interleukin-10 and tumor necrosis factor in individuals with oral lichen planus. J Oral Pathol Med 36:476–481
29. Ding M, Xu JY, Fan Y (2010) Altered expression of mRNA for HIF-1alpha and its target genes RTP801 and VEGF in patients with oral lichen planus. Oral Dis 16:299–304
30. Parra FC, Amado RC, Lambertucci JR, Rocha J, Antunes CM, Pena SD (2003) Color and genomic ancestry in Brazilians. Proc Natl Acad Sci U S A 100:177–182
31. Pimenta JR, Zuccherato LW, Debes AA, Maselli L, Soares RP, Moura-Neto RS et al (2006) Color and genomic ancestry in Brazilians: a study with forensic microsatellites. Hum Hered 62:190–195
32. Boom R, Sol CJ, Salimans MM, Jansen CL, Wertheim-van Dillen PM, van der Noordaa J (1990) Rapid and simple method for purification of nucleic acids. J Clin Microbiol 28:495–503
33. Farias LC, Fraga CA, De Oliveira MV, Silva TF, Marques-Silva L, Moreira PR et al (2010) Effect of age on the association between p16CDKN2A methylation and DNMT3B polymorphism in head and neck carcinoma and patient survival. Int J Oncol 37:167–176
34. Correa GT, Bandeira GA, Cavalcanti BG, de Carvalho Fraga CA, Dos Santos EP, Silva TF et al (2011) Association of -308 TNF-alpha promoter polymorphism with clinical aggressiveness in patients with head and neck squamous cell carcinoma. Oral Oncol 47:888–894
35. Fonseca-Silva T, Farias LC, Cardoso CM, Souza LR, Carvalho Fraga CA, Oliveira MV et al (2012) Analysis of p16(CDKN2A) methylation and HPV-16 infection in oral mucosal dysplasia. Pathobiology 79:94–100
36. Mignogna MD, Fedele S, Lo RL, Mignogna C, de Rosa G, Porter SR (2007) Field cancerization in oral lichen planus. Eur J Surg Oncol 33:383–389
37. Mithani SK, Mydlarz WK, Grumbine FL, Smith IM, Califano JA (2007) Molecular genetics of premalignant oral lesions. Oral Dis 13:126–133
38. Semenza GL (2003) Targeting HIF-1 for cancer therapy. Nat Rev Cancer 3:721–732
39. Semenza GL (2004) Hydroxylation of HIF-1: oxygen sensing at the molecular level. Physiology (Bethesda) 19:176–182
40. Semenza GL, Shimoda LA, Prabhakar NR (2006) Regulation of gene expression by HIF-1. Novartis Found Symp 272:2–8
41. Scardina GA, Ruggieri A, Messina P, Maresi E (2009) Angiogenesis of oral lichen planus: a possible pathogenetic mechanism. Med Oral Patol Oral Cir Bucal 14:e558–62
42. Scardina GA, Ruggieri A, Maresi E, Messina P (2011) Angiogenesis in oral lichen planus: an in vivo and immunohistological evaluation. Arch Immunol Ther Exp (Warsz) 59:457–62
43. An HJ, Lee H, Paik SG (2011) Silencing of BNIP3 results from promoter methylation by DNA methyltransferase 1 induced by the mitogen-activated protein kinase pathway. Mol Cells 31:579–83
44. Mizuno S, Chijiwa T, Okamura T, Akashi K, Fukumaki Y, Niho Y et al (2001) Expression of DNA methyltransferases DNMT1, 3A, and 3B in normal hematopoiesis and in acute and chronic myelogenous leukemia. Blood 97:1172–1179
45. Montgomery KG, Liu MC, Eccles DM, Campbell IG (2004) The DNMT3B C– > T promoter polymorphism and risk of breast cancer in a British population: a case–control study. Breast Cancer Res 6:R390–R394
46. Nagai M, Nakamura A, Makino R, Mitamura K (2003) Expression of DNA (5-cytosin)-methyltransferases (DNMTs) in hepatocellular carcinomas. Hepatol Res 26:186–191
47. Patra SK, Patra A, Zhao H, Dahiya R (2002) DNA methyltransferase and demethylase in human prostate cancer. Mol Carcinog 33:163–171
48. Fonseca-Silva T, Oliveira MV, Fraga CA, Farias LC, Gomes EP, Barros LO et al (2012) DNMT3B (C46359T) polymorphisms and immunoexpression of DNMT3b and DNMT1 proteins in oral lichen planus. Pathobiology 79:18–23
49. van der Flier M, Geelen SP, Kimpen JL, Hoepelman IM, Tuomanen EI (2003) Reprogramming the host response in bacterial meningitis: how best to improve outcome? Clin Microbiol Rev 16:415–29