To study high mobility group protein B1 (HMGB1) and nuclear transcription factor p65 (NF-κB p65) expression in non-small cell lung cancer and its significance.

Material and methods: 106 hospitalized patients with non-small cell lung cancer after thoracic surgery were enrolled; HMGB1 and p65 protein expression was detected by the immunohistochemical method. Semiquantitative expression of HMGB1 and NF-κB p65 was analyzed using Image Pro Plus (IPP) software and statistical analysis.

Results: The rate of HMGB1 positive expression in the non-small cell lung cancer protein B1 family was significantly higher than normal tissues ($P < 0.05$); p65 protein expression in the non-small cell lung carcinoma group was significantly higher than that of normal tissues ($P < 0.05$). HMGB1 and NF-κB p65 protein expression was significantly higher compared with the non-metastatic group ($P < 0.01$). HMGB1 and NF-κB p65 protein expression showed a positive correlation ($P < 0.05$).

Conclusions: HMGB1 and NF-κB p65 expression may be related to non-small cell lung cancer metastasis.

Key words: non-small cell lung cancer, high mobility group protein B1, nuclear transcription factor p65, transfer, immunohistochemistry.

Expression of HMGB1 and NF-κB p65 and its significance in non-small cell lung cancer

Xiaohong Zhang, Hongmin Wang, Jing Wang

1Department of Respiratory Medicine, Central Hospital of Zhengzhou, Zhengzhou, China
2Department of Respiratory Medicine, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Introduction

Lung cancer is one of the most common malignancies in the world. In recent years, its incidence and mortality keep rising, and the survival rate is as poor as 12.5% [1–4]. Results of the study in the Polish population confirmed the efficacy of erlotinib in advanced NSCLC after failure of prior platinum-based chemotherapy [5]. High mobility group protein B1 (HMGB1), a non-histone chromosomal protein in eukaryotic cells, correlates highly with invasion and metastasis in multiple tumors. As revealed by previous research, tumor exogenous may be enhanced by HMGB1, which improves the production ratio of matrix metalloproteinases-9 (MMP9) and optimizes MMP9 gene activity, through activating p65 protein, one of the nuclear transcription factors, and adhering to the key site of the MMP9 gene [6–9]. The p53 gene and protein are significant in the elimination of impaired cells, through the path of apoptosis. In the mutation of the p53 gene, abnormal p53 protein is created. The biggest number of cells which accumulate protein p53 has been disclosed in the cells of adenocarcinoma whereas the smallest number of cells which accumulate protein p53 has been disclosed in multicellular types of cancer, and a smaller number of cells accumulating protein p53 has been disclosed in older patients [10].

With a sample including 106 non-small cell lung cancer (NSCLC) patients, we carried out a pathological study on content of p65 protein, the nuclear transcription factor, and HMGB1, to analyze their correlation with various clinical parameters, and discuss their effects on the enhanced exotrophy in NSCLC. Our results are presented here.

Material and methods

Clinical data

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants. This retrospective research included 106 NSCLC patients in hospitalized by our hospital from February 2009 to February 2011, 76 males and 30 females, aged between 32 and 80 years, average 60.2 y. All patients underwent thoracotomy, without neo-adjuvant chemotherapy or radiotherapy.

Immunohistochemistry

Routine paraffin sectioning, dewaxing, and hydration using 3% hydrogen peroxide were performed to remove endogenous peroxidase. Microwave antigen was retrieved and blocked with fetal calf serum for 2 h. About 50 µl (1:25) of goat polyclonal anti-human HMGB1 and NF-κB p65 were added, and the mixture was incubated at 4°C overnight. About 50 µl of biotinylated goat
anti-rabbit IgG secondary antibody working solution was added, and the mixture was incubated at 37°C for 30 min, followed by dianinobenzidine coloration. The sample was dyed with hematoxylin, separated using ethanol and hydrochloric acid, saturated with lithium carbonate until the color returned to blue, and then dehydrated with gradient alcohol as well as xylene. Mounting with neutral resin followed. The negative control used was PBS in place of the primary antibody.

In immunohistochemistry (IMC) SP, the sample appearing yellow or brownish yellow was considered as positive. Quantity and intensity of the stained cells were evaluated by the staining in each of ten fields in 400-fold magnification for 100 cells per observation. A sample was scored 0 for positive cells below 10%, 1 for 11–25%, 2 for 26–50%, 3 for 51–75%, and 4 for higher than 75%. Microscopic staining intensity for the positively stained cells was scored 1 for the yellow, 2 for the brownish yellow, and 3 for the brown. The final observation result, a product of the percentage of the positive cells out of those under observation multiplied by the staining intensity, was considered as negative for the product 0, which means no less than 10% positive cells were found, weak positive for 1–4, which means the average number of positive cells was less than 25%, moderate positive for 5–8, which means the average number of positive cells was less than 50%, and strong positive for 9–12, which means the average number of positive cells was more than 50%, wherein the former two were regarded as low expression in HMGB1, and the latter two as high expression.

Statistical analysis

Semiquantitative expression of NF-κB p65 and HMGB1 was analyzed by the score. Only 0 was negative, while others were all considered as positive. χ² test was conducted to test the relevance of the expression of NF-κB p65 (or HMGB1) and the tumor size, histomorphological types, tumor mesenchyme, differentiation degree and lymph node metastasis. Meanwhile, the relation between NF-κB p65 and HMGB1 was also evaluated with χ². P < 0.05 was considered as a significant difference.

Results

Clinical data

The clinical data are shown in Table 1. The patients included 65 squamous carcinomas, 25 adenocarcinomas, 16 adenosquamous carcinomas, 64 with node metastasis and 42 without, 36 in stage I, 22 in stage II and 48 in stage III, 50 poorly differentiated, 39 moderately differentiated and 17 well differentiated. Paracarcinomatous tissue beyond 5 cm from the tumor margin was collected from 32 patients during the operation as the control.

Expression of HMGB1 and p65

High expression of HMGB1 was found in both cytoplasm and nucleus of both tumor cells and interstitial inflammatory cells. Expression of the nuclear transcription factor p65 was noted in cytoplasm and nucleus of tumor cells with the intensity from faint yellow to brownish yellow, but generally null in the interstitial cells. Positive expression of either HMGB1 (p < 0.05) or p65 (p < 0.01) was higher significantly in NSCLC tissue than in the control, the paracarcinomatous tissue. The expressed quantity of either HMGB1 or p65 was significantly higher in patients with node metastasis than in those without it (p < 0.01).

Correlation analysis

Expression of p65 was observed in 36 (70.59%) out of 51 NSCLC tumor tissues high in HMGB1 expression, and in only 12 (21.81%) out of 55 low in HMGB1, and there was a relation between NF-κB p65 and HMGB1 (p < 0.05).

Discussion

Prognosis highly correlates with metastasis in lung cancer patients. HMGB1 was first discovered to be an omnipresent DNA-binding protein, which regulates the genesis of transcription complex and therefore participates in the transcription, replication and repair of DNA and cellular mobility, through inducing the transfiguration of chromosomes and DNA [11–15]. Secreted by macrophages, monocytes or damaged necrotic cells, HMGB1 induces a chemotactic response, and therefore participates in metastasis of tumor cells [16–18]. HMGB1 in 95D human lung cancer cells, HMGB1 alone or acting synergistically with CpG ODN could enhance the progression of 95D cells, which would promote the progression of lung cancer [19]. Our research revealed its high expression in tumor cells and interstitial cells, and significantly higher expression in tumors with node metastasis than in those without it, which seems similar to the results of previous research on cervix cancer and colon cancer, implying a correlation between positive HMGB1 expression and node metastasis in NSCLC.

P65 protein, a transcription factor first separated from materials contained in the nucleus of mature immune cells, is a molecule involved in cellular signal transduction, which influences the activity of transcription factors through various mechanisms, by all means, in all ways, and therefore intensifies or attenuates cellular functions or activities in different stages of the life cycle [20, 21]. Skeletal metastases are a frequent complication of lung cancer, and p65 was one of the signal proteins involved in the skeletal complications of cancer metastases [22]. Therefore, p65 became one of the foci in research on mechanisms involved in oncogenesis. Fujikake et al. revealed a positive correlation between the transcription factor p65 and tumor metastasis. It has been confirmed in pulmonary cancer that RelA/p65 is necessary to link smoke-induced inflammation and has a role in the activation of Wnt/β-catenin signaling in tumor cells [23]. In our research, expression of p65 was found positive in cytoplasm and nucleus of tumor cells but null generally in the interstitial cells. Furthermore, significantly higher expression of both HMGB1 and p65 was observed in tumors with node metastasis than in those without it, implying a certain close correlation between tumor metastasis and HMGB1.

This research also suggests that there is a positive correlation between HMGB1 and the transcription factor p65 in NSCLC. Some other research found that HMGB1 and p65 were important factors in melanoma progression [24]. Therefore,
Table 1. Relationship between HMGB1, NF-κB p65 expression and the clinic pathological features of NSCLC

| Clinic pathological parameters | n  | NF-κB p65 positive expression [cases (%)] | x² value | P value | HMGB1 positive expression [cases (%)] | x² value | P value |
|-------------------------------|----|------------------------------------------|----------|---------|--------------------------------------|----------|---------|
| Tumor size                    |    |                                          |          |         |                                      |          |         |
| ≤ 3 cm                        | 48 | 21 (43.75)                               | 0.007    | 0.929   | 28 (47.92)                          | 0.027    | 0.849   |
| > 3 cm                        | 58 | 26 (44.83)                               |          |         | 28 (48.28)                          |          |         |
| Histomorphological types      |    |                                          |          |         |                                      |          |         |
| Squamous cancer               | 65 | 22 (33.80)                               |          |         | 25 (38.46)                          | 0.009    | 0.934   |
| Adenocarcinoma                | 25 | 14 (56.00)                               | 9.386    | 0.009   | 16 (64.00)                          | 6.97     | 0.035   |
| Adenosquamous carcinoma       | 16 | 12 (75.00)                               |          |         | 11 (69.00)                          |          |         |
| Tumor mesenchyme              |    |                                          |          |         |                                      |          |         |
| Squamous carcinoma            | 65 | 0                                        |          |         | 51 (78.46)                          |          |         |
| Adenocarcinoma                | 25 | 0                                        |          |         | 10 (40.00)                          | 0.003    | 0.941   |
| Differentiation degree        |    |                                          |          |         |                                      |          |         |
| Low                           | 50 | 29 (58.00)                               |          |         | 31 (62.00)                          |          |         |
| Median                        | 39 | 13 (33.03)                               | 7.084    | 0.028   | 16 (41.03)                          | 7.647    | 0.021   |
| High                          | 17 | 4 (23.53)                                |          |         | 4 (23.53)                           |          |         |
| Lymph node metastasis         |    |                                          |          |         |                                      |          |         |
| Yes                           | 64 | 38 (59.38)                               |          |         | 42 (65.63)                          |          |         |
| No                            | 42 | 9 (21.43)                                | 12.438   | 0.000   | 9 (21.43)                           | 17.258   | 0.000   |

Note: HMGB1: nuclear transcription factor protein B1; NF-κB p65: Nuclear transcription factor p65 protein

NF-κB p65

| Tumor size | Positive | Negative | Total |
|------------|----------|----------|-------|
| < 3 cm     | 21 (a)   | 27 (b)   | 48 (a + b) |
| ≥ 3 cm     | 26 (c)   | 32 (d)   | 58 (c + d) |
| Total      | 47 (a + c) | 59 (b + d) | 106 (n) |

\[
T_{11} = (a + b) \times (a + c)/n = 48 \times 47/106 = 21.28 > 5;
T_{12} = (a + b) \times (b + d)/n = 28 \times 59/106 = 16.40 > 5;
T_{22} = (c + d) \times (b + d)/n = 48 \times 59/106 = 29.43 > 5;
\]

\[
x^2 = (a - T_{11})^2/T_{11} + (b - T_{12})^2/T_{12} + (c - T_{21})^2/T_{21} + (d - T_{22})^2/T_{22} = 0.0012;
\]

\[
P = 0.7
\]

HMGB1

| Tumor size | Positive | Negative | Total |
|------------|----------|----------|-------|
| ≥ 3 cm     | 23 (a)   | 25 (b)   | 48 (a + b) |
| < 3 cm     | 28 (c)   | 30 (d)   | 58 (c + d) |
| Total      | 51 (a + c) | 55 (b + d) | 106 (n) |

\[
T_{11} = (a + b) \times (a + c)/n = 48 \times 51/106 = 23.09 > 5;
T_{12} = (a + b) \times (b + d)/n = 24.91 > 5;
T_{22} = (c + d) \times (b + d)/n = 27.91 > 5;
\]

\[
x^2 = (a - T_{11})^2/T_{11} + (b - T_{12})^2/T_{12} + (c - T_{21})^2/T_{21} + (d - T_{22})^2/T_{22} = 0.0012;
\]

\[
P = 0.7
\]

NF-κB p65

| Histomorphological types | Positive | Negative | Total |
|--------------------------|----------|----------|-------|
| Squamous cancer          | 22       | 43       | 65    |
| Adenocarcinoma           | 14       | 11       | 25    |
| Adenosquamous carcinoma  | 12       | 4        | 16    |
| Total                    | 48       | 58       | 106   |

\[
T_{11} = 65 \times 48/106 = 29.43 > 5;
T_{12} = 65 \times 58/106 = 35.57 > 5;
T_{22} = 25 \times 48/106 = 11.32 > 5;
\]

\[
x^2 = (a - T_{11})^2/T_{11} + (b - T_{12})^2/T_{12} + (c - T_{21})^2/T_{21} + (d - T_{22})^2/T_{22} = 10.2928;
\]

\[
P = 0.05 < p < 0.01
\]
Table 1 Cont.

**HMGB1**

| Histomorphological types          | Positive | Negative | Total |
|-----------------------------------|----------|----------|-------|
| Squamous cancer                   | 25       | 40       | 65    |
| Adenocarcinoma                    | 16       | 9        | 25    |
| Adenosquamous carcinoma           | 11       | 5        | 16    |
| Total                             | 52       | 54       | 106   |

\[ n = 106; \]
\[ T_{11} = \frac{65 \times 52}{106} = 31.89 > 5; \]
\[ T_{12} = \frac{65 \times 54}{106} = 33.11 > 5; \]
\[ T_{21} = \frac{25 \times 52}{106} = 12.26 > 5; \]
\[ T_{22} = \frac{25 \times 54}{106} = 12.74 > 5; \]
\[ x^2 = 106 \left( \frac{25^2}{65 \times 52} + \frac{40^2}{65 \times 54} + \frac{16^2}{52 \times 25} + \frac{9^2}{54 \times 25} + \frac{11^2}{52 \times 16} + \frac{5^2}{54 \times 16} \right) - 1 = 35.24; \]
\[ P < 0.005. \]

**NF-κB p65**

| Differentiation degree | Positive | Negative | Total |
|------------------------|----------|----------|-------|
| Low                    | 29       | 21       | 50    |
| Median                 | 13       | 26       | 39    |
| High                   | 4        | 13       | 17    |
| Total                  | 46       | 60       | 106   |

\[ n = 106; \]
\[ T_{11} = \frac{50 \times 46}{106} = 21.70 > 5; \]
\[ T_{12} = \frac{50 \times 60}{106} = 28.30 > 5; \]
\[ T_{21} = \frac{39 \times 46}{106} = 16.92 > 5; \]
\[ T_{22} = \frac{39 \times 60}{106} = 17.66 > 5; \]
\[ x^2 = 106 \left( \frac{31^2}{50 \times 46} + \frac{19^2}{50 \times 60} + \frac{16^2}{39 \times 46} + \frac{23^2}{39 \times 60} + \frac{4^2}{17 \times 46} + \frac{13^2}{17 \times 60} \right) - 1 = 8.6746; \]
\[ V = (2 – 1) 	imes (3 – 1) = 2; \]
\[ P < 0.025. \]

**HMGB1**

| Differentiation degree | Positive | Negative | Total |
|------------------------|----------|----------|-------|
| Low                    | 31       | 19       | 50    |
| Median                 | 16       | 23       | 39    |
| High                   | 4        | 13       | 17    |
| Total                  | 51       | 55       | 106   |

\[ n = 106; \]
\[ T_{11} = \frac{50 \times 52}{106} = 24.06 > 5; \]
\[ T_{12} = \frac{50 \times 55}{106} = 25.94 > 5; \]
\[ T_{21} = \frac{39 \times 52}{106} = 18.76 > 5; \]
\[ T_{22} = \frac{39 \times 55}{106} = 20.24 > 5; \]
\[ x^2 = 106 \left( \frac{31^2}{50 \times 52} + \frac{19^2}{50 \times 55} + \frac{16^2}{39 \times 52} + \frac{23^2}{39 \times 55} + \frac{4^2}{17 \times 52} + \frac{13^2}{17 \times 55} \right) - 1 = 8.7615; \]
\[ V = (2 – 1) 	imes (3 – 1) = 2; \]
\[ P < 0.025. \]

**NF-κB p65**

| Lymph node metastasis | Positive | Negative | Total |
|-----------------------|----------|----------|-------|
| Yes                   | 38 (a)   | 26 (b)   | 64 (a + b) |
| No                    | 9 (c)    | 33 (d)   | 42 (c + d) |
| Total                 | 47 (a + c) | 59 (b + d) | 106 (n) |

\[ n = 106 > 40; \]
\[ T_{11} = \frac{(a + b) \times (a + c)}{n} = \frac{64 \times 47}{106} = 29.38 > 5; \]
\[ T_{12} = \frac{(a + b) \times (b + d)}{n} = \frac{64 \times 59}{106} = 35.62 > 5; \]
\[ T_{21} = \frac{(c + d) \times (a + c)}{n} = \frac{42 \times 47}{106} = 18.62 > 5; \]
\[ T_{22} = \frac{(c + d) \times (b + d)}{n} = \frac{42 \times 59}{106} = 23.38 > 5; \]
\[ x^2 = \frac{(a - T_{11})^2}{T_{11}} + \frac{(b - T_{12})^2}{T_{12}} + \frac{(c - T_{21})^2}{T_{21}} + \frac{(d - T_{22})^2}{T_{22}} = 13.9298; \]
\[ V = 1; \]
\[ P < 0.005. \]
we speculate that these two molecules might not only be adopted as markers in a joint detection to help evaluate the prognosis of NSCLC patients, but also regarded as potential targets under investigation in cancer therapy.

The authors declare no conflict of interest.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.
2. Whitson BA, Groth SS, Duval SJ, Swanson SJ, Maddaus MA. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg 2008; 86: 2008-16.
3. Endo C, Sagawa M, Sakurada A, Sato M, Kondo T, Fujimura S. Surgical treatment of stage I non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg 2003; 9: 283-9.
4. Kang R, Tang D, Schapiro NE, et al. The receptor for advanced glycation end products (RAGE) sustains autophagy and limits apoptosis, promoting pancreatic tumor cell survival. Cell Death Differ 2010; 17: 666-76.
5. Kowalski DM, Krzakowski M, Ramlau R, Jaskiewicz P, Janowicz-Żebrowska A. Erlotinib in salvage treatment of patients with advanced non-small cell lung cancer: results of an expanded access programme in Poland. Wspolczesna Onkol 2012; 16: 170-5.
6. Kew RR, Penzo M, Habelt DM, Marcu KB. The IKKα-dependent NF-κB p52/RelB noncanonical pathway is essential to sustain a CXCL12 autocrine loop in cells migrating in response to HMGB1. J Immunol 2012; 188: 2390-6.
7. Fiuza C, Bustin M, Talwar S, et al. Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. Blood 2003; 101: 2652-60.
8. van Beijnum JR, Buurman WA, Griffioen AW. Convergence and amplification of toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signaling pathways via high mobility group B1 (HMGB1). Angiogenesis 2008; 11: 91-9.
9. Hasegawa N. Effect of high mobility group box 1 (HMGB1) in cultured human periodontal ligament cells. Kokubyo Gakkai Zassi 2008; 75: 155-61.
10. Wyrobiec G, Rokicki W, Štěpěšková K, Kasperszcyk J, Štepěř-Šyrobiec O, Sabat D, Helewski K. Protein p53 in non-small lung carcinomas. Pol J Cardiol 2008; 55: 4-24.
11. Wang H, Yang H, Tracey KJ. Extracellular role of HMGB1 in inflammation and sepsis. J Intern Med 2004; 255: 320-31.
12. Sims GP, Rowe DC, Rietjens ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol 2010; 28: 367-88.
13. Volz HC, Kaya Z, Katus HA, Andrassy M. The role of HMGB1/RAGE in inflammatory cardiomypathy. Semin Thromb Hemost 2010; 36: 185-94.
14. Huang W, Tang Y, Li L. HMGB1, a potent proinflammatory cytokine in sepsis. Cytokine 2010; 51: 119-26.
15. Sasahira T, Kirita T, Oue N, et al. High mobility group box-1-inducible melanoma inhibitory activity is associated with nodal metastasis and lymphangiogenesis in oral squamous cell carcinoma. Cancer Sci 2008; 99: 1806-12.
16. Rauvala H, Rauhainen A. Physiological and pathophysiological outcomes of the interactions of HMGB1 with cell surface receptors. Biochim Biophys Acta 2010; 1799: 164-70.
17. Pereira-Machado JA, Voog JM, Veloso CA, Chaves MM. HMGB1, TLR and RAGE: a functional tripod that leads to diabetic inflammation. Expert Opin Ther Targets 2011; 15: 1023-35.
18. Sen R, Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell 1986; 46: 705-16.
19. Wang C, Fei G, Liu Z, Li Q, Xu Z, Ren T. HMGB1 was a pivotal synergistic effector for CpG oligonucleotides to enhance the progression of human lung cancer cells. Cancer Biol Ther 2012; 13: 727-36.

Table 1. Cont

| Lymph node metastasis | Positive | Negative | Total |
|-----------------------|----------|----------|-------|
| Yes                   | 42 (a)   | 22 (b)   | 64 (a + b) |
| No                    | 9 (c)    | 33 (d)   | 42 (c + d) |
| Total                 | 51 (a + c) | 55 (b + d) | 106 (n) |

n = 106 > 40

\[ T_1 = (a + b) \times (a + c)/n = 64 \times 51/106 = 30.79 > 5; \]
\[ T_2 = (a + b) \times (b + d)/n = 64 \times 55/106 = 33.21 > 5; \]
\[ T_3 = (c + d) \times (a + c)/n = 42 \times 51/106 = 20.21 > 5; \]
\[ T_4 = (c + d) \times (b + d)/n = 42 \times 55/106 = 21.79 > 5; \]
\[ \chi^2 = (a - T_1)^2/T_1 + (b - T_3)^2/T_3 + (c - T_2)^2/T_2 + (d - T_4)^2/T_4 = 19.8502; \]
\[ v = 2; \]
\[ P < 0.005 \]

Relation between p65 and HMGB1

| p65 (+) | HMGB1 (+) | HMGB1 (-) | Total |
|---------|-----------|-----------|-------|
| 36 (a)  | 12 (b)    | 48 (a + b)|       |
| 15 (c)  | 43 (d)    | 58 (c + d)|       |
| Total   | 51 (a + c)| 55 (b + d)| 106 (n) |

n = 106 > 40

\[ T_1 = (a + b) \times (a + c)/n = 48 \times 51/106 = 23.09 > 5; \]
\[ T_2 = (a + b) \times (b + d)/n = 24.91 > 5; \]
\[ T_3 = (c + d) \times (a + c)/n = 27.91 > 5; \]
\[ T_4 = (c + d) \times (b + d)/n = 29.09 > 5; \]
\[ \chi^2 = (a - T_1)^2/T_1 + (b - T_3)^2/T_3 + (c - T_2)^2/T_2 + (d - T_4)^2/T_4 = 25.4196; \]
\[ v = 2; \]
\[ P < 0.005 \]
20. Ruan Q, Chen YH. Nuclear factor-κB in immunity and inflammation: the Treg and Th17 connection. Adv Exp Med Biol 2012; 946: 207-21.
21. Fujioka S, Sclabas GM, Schmidt C, et al. Function of nuclear factor kappaB in pancreatic cancer metastasis. Clin Cancer Res 2003; 9: 346-54.
22. Schulze J, Weber K, Baranowsky A, et al. p65-Dependent production of interleukin-1β by osteolytic prostate cancer cells causes an induction of chemokine expression in osteoblasts. Cancer Lett 2012; 317: 106-13.
23. Li D, Beisswenger C, Herr C, et al. Myeloid cell RelA/p65 promotes lung cancer proliferation through Wnt/β-catenin signaling in murine and human tumor cells. Oncogene 2013 Apr 8. doi: 10.1038/onc.2013.75 [Epub ahead of print].
24. Poser I, Golob M, Buettner R, Bosserhoff AK. Upregulation of HMG1 leads to melanoma inhibitory activity expression in malignant melanoma cells and contributes to their malignancy phenotype. Mol Cell Biol 2003; 23: 2991-8.

Address for correspondence
Prof. Hongmin Wang
The First Affiliated Hospital of Zhengzhou University
No. 1 Jianshedong Road Erqi District
Zhengzhou 450052, China
tel. 86-0371-66913345
e-mail: hmxhcn@163.com

Submitted: 4.04.2012
Accepted: 8.05.2013