Association between survivin genetic polymorphisms and epidermal growth factor receptor mutation in non–small-cell lung cancer

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Received: 2016.07.17; Accepted: 2016.09.27; Published: 2016.11.23

Abstract

Survivin is an anti-apoptotic protein that is implicated in the regulation of apoptosis and cell cycle in various types of cancers. The current study explored the effect of survivin gene polymorphisms and EGFR mutations in non-small-cell lung carcinoma (NSCLC) patients. A total of 360 participants, including 291 adenocarcinoma lung cancer and 69 squamous cell carcinoma lung cancer patients, were selected for the analysis of three survivin genetic variants (survivin -31, +9194, and +9809) by using real-time PCR genotyping. The results indicated that GC+CC genotypes of survivin -31 were significant association with EGFR mutation in lung adenocarcinoma patients (adjusted odds ratio=3.498, 95% CI = 1.171-10.448; p<0.01). Moreover, The GC+CC genotypes of survivin -31 were associated with EGFR L858R mutation but not in exon 19 in-frame deletions. Furthermore, among patients in exon 19 in-frame deletions, those who have at least one polymorphic G allele of survivin -31 have an increased incidence to develop late-stage when compared with those patients homozygous for C/C (OR, 4.800; 95% CI, 1.305-17.658). In conclusion, our results showed that survivin genetic variants were related to EGFR mutation in lung adenocarcinoma patients and might contribute to pathological development to NSCLC.

Key words: non-small-cell lung carcinoma; survivin; epidermal growth factor receptor; genetic variants.

Introduction

The lung cancer is the leading cause of death worldwide. In 2009, molecular target therapy such as epidermal growth factor receptor (EGFR) inhibitors was recognized as a potential treatment for certain types of lung cancer [1, 2]. The effect of EGFR tyrosine kinase inhibitors (EGFR-TKI) has been linked to EGFR mutations in cancer cells, most of which are exon 19 deletions followed by exon 21 L858R mutations [3-5]. Current studies on EGFR mutations have shown a higher tendency of EGFR mutations in adenocarcinoma, such as in female cancer patients with no smoking history [6-8]. Regarding racial differences in EGFR mutations, EGFR mutations have been observed in approximately 12%-15% of...
Caucasian patients with lung adenocarcinoma, but the rate can be as high as 60% in Asian populations [5, 9]. For EGFR-TKIs, the most frequently studied drugs are gefitinib and erlotinib [4, 10]. Nevertheless, even in patients with EGFR mutations, the treatment efficacy of these drugs is only approximately 60%-70% [11]. Therefore, identifying biomarkers that enhance the treatment efficacy of these drugs is crucial.

Survivin, also known as BIRC6, located on human chromosome 17q2, is a member of the inhibitors of apoptosis protein (IAP) family and its key function is apoptosis suppression [12, 13]. Researchers have found that in the mitochondria, survivin directly suppresses Bax- and Fas-induced apoptosis and blocks the apoptosis pathway by binding to activated caspase-3 and caspase-7 proteins [14, 15]. In addition to apoptosis suppression, an increasing number of studies are showing that survivin is tumor-specific because it is expressed in large quantities in tumor tissues and is closely associated with tumor differentiation, proliferation, and metastasis [16, 17]. In non-small-cell lung cancer (NSCLC), high expression of survivin indicates a poor clinical prognosis [18-20]. Other studies have suggested that suppressing survivin in lung cancer cells can reduce lung cancer metastasis and invasion [21-23]. Some researchers have indicated that in EGFR-mutated lung cancer cell lines, EGFR-TKIs may induce apoptosis by suppressing survivin expression [24-26]. A study by Shi showed that survivin expression in the blood is a reliable marker of EGFR-TKI treatment efficacy in patients with lung cancer [26].

Some studies have reported that single nucleotide polymorphism (SNP) of survivin promoters alters protein expression by affecting the functions of transcription factors [27-29]. In fact, the SNP of survivin influences the severity and prognosis of many types of cancer including stomach, colorectal, and lung cancer [27, 30-32]. Although the SNP of survivin -31 G/C and other SNPs that can affect survivin expression, the association between the SNP of survivin and EGFR mutations in NSCLC still needs to be verified. Moreover, the high EGFR mutation rate, including L858R in exon 21 or in-frame deletion in exon 19, was found in Taiwan populations. Therefore, the present study examined the association between survivin SNP and EGFR mutations and explored the association between survivin SNP and the clinicopathological characteristics in NSCLC.

Methods

Patient Specimens
In 2012-2014, we recruited 360 patients with lung cancer, including 291 adenocarcinoma lung cancer and 69 squamous cell carcinoma lung cancer patients, at Cheng-Ching General Hospital in Taichung, Taiwan. Demographic characteristics and medical information of the patients, including TNM clinical staging, primary tumor size, lymph node involvement, and histologic grade, was obtained from their medical records. Exons 18-21 of the EGFR gene were amplified using polymerase chain reaction and subsequently sequenced as described previously [33]. This study was approved by the Institutional Review Board of Cheng-Ching General Hospital (No: HP120009) and informed consent was obtained from all subjects.

Genomic DNA extraction and survivin genotyping
DNA was extracted from buffy coats using a QIAaamp DNA blood mini kits (Qiagen, Valencia, California) as described in detail previously [34]. DNA was dissolved in TE buffer and used as the template in polymerase chain reactions. Allelic discrimination of survivin -31, +9194, and +9809 gene polymorphism was assessed with the ABI StepOne™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and analyzed using SDS vers. 3.0 software (Applied Biosystems), with the TaqMan assay [28, 29].

Statistical analysis
The distributions of demographic characteristics and genotype frequencies between adenocarcinoma lung cancer and squamous cell carcinoma lung cancer as well as clinicopathological features in different genotypes were analyzed by χ²-test. The odds ratio and 95% CIs of the association between the genotype frequencies and EGFR mutation risk and the clinical pathological characteristics were estimated using multiple logistic regression models after controlling for other covariates. A p value of <0.05 was considered statistically significant. The data were analyzed with SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Results
Patients’ characteristics and distribution of lung cancer
Total 360 patients were enrolled in this study. The demographics and clinical characteristics of patients were shown in Table 1. The average age of patients was 66 years. The gender distribution in patients were 205 male (56.9%) and 155 female (44.5%). In all patients, the percentage of adenocarcinoma and squamous cell carcinoma were 80.8% (291/360) and 19.2% (69/360), respectively.
Moreover, female patients possessed higher frequency (male vs. female = 49.5% vs. 50.5%) in the adenocarcinoma. For the cigarette smoking status, it was shown 58.6% (205/360) never-smokers and 41.4% (149/360) ever-smokers. Furthermore, never-smoking patients had higher frequency (never-smokers vs. ever-smokers = 66.7% vs. 33.3%) in the adenocarcinoma, while it was shown lower frequency (never-smokers vs. ever-smokers = 24.6% vs. 75.4%) in the squamous cell carcinoma (p<0.001).

Associations between survivin SNPs and lung cancer

The distribution frequency of survivin -31, +9194 and +9809 genotypes in the lung adenocarcinoma and squamous cell carcinoma are shown in Table 2. The alleles with the highest distribution frequency for -31, +9194 and +9809 of survivin in recruited patients with NSCLC were heterozygous C/G, homozygous A/A, and heterozygous T/C, respectively. After adjusting variables, there was no significant difference between the lung adenocarcinoma and squamous cell carcinoma with polymorphisms of the survivin -31, +9194 and +9809 genotypes when compared with wild-type individuals.

Table 2. Distribution frequency of survivin genotypes in 291 lung adenocarcinoma and 69 lung squamous cell carcinoma.

| Variable | adenocarcinoma (N=291) (%) | squamous cell carcinoma (N=69) (%) | OR (95% CI) | AOR (95% CI) |
|----------|---------------------------|----------------------------------|-------------|--------------|
| survivin -31 | | | | |
| CC       | 91 (31.3%)                | 22 (31.9%)                       | 1.00        | 1.00         |
| CG       | 137 (47.1%)               | 30 (43.5%)                       | 0.906       | 0.776        |
| GG       | 63 (21.6%)                | 17 (24.6%)                       | 1.014       | 0.825        |
| AG+GG    | 200 (68.7%)               | 47 (68.1%)                       | 0.972       | 0.792        |
| survivin +9194 | | | | |
| AA       | 172 (59.1%)               | 43 (62.3%)                       | 1.00        | 1.00         |
| AG       | 98 (33.7%)                | 19 (27.5%)                       | 0.776       | 1.291        |
| GG       | 21 (7.2%)                 | 7 (10.1%)                        | 1.333       | 3.031        |
| AG+GG    | 119 (40.9%)               | 26 (37.7%)                       | 0.874       | 1.627        |
| survivin +9809 | | | | |
| TT       | 106 (37.1%)               | 25 (36.2%)                       | 1.00        | 1.00         |
| TC       | 132 (45.4%)               | 27 (39.1%)                       | 0.884       | 0.864        |
| CC       | 51 (17.5%)                | 17 (24.7%)                       | 1.440       | 0.763        |
| TC+CC    | 183 (62.9%)               | 44 (63.8%)                       | 1.039       | 0.831        |

The AORs with 95% CIs were estimated by multiple logistic regression models after controlling for age, gender and cigarette smoking status.

Patient’s characteristics and distribution of EGFR mutations in adenocarcinoma

We further investigated the associations between EGFR mutations and patient’s characteristics. As shown in Table 3, both substitution mutation (L858R) and Exon 19 in-frame deletion mutations were shown higher percentage in female patients (male vs. female = 19.2% vs. 80.8% and 44.9% vs. 55.1%, respectively) and in never-smoker patients (never-smokers vs. ever-smokers = 88.5% vs.11.5% and 73.5% vs. 26.5%, respectively). The data of distribution were shown in never-smoker patients (never-smokers vs. ever-smokers = 88.5% vs.11.5% and 73.5% vs. 26.5%, respectively). The data of distribution were shown significantly different between control (wild-type) and EGFR mutations in gender (p<0.05) and cigarette smoking status (p<0.05). These results indicated that EGFR mutations were associated with gender and cigarette smoking status.

Associations between survivin SNPs and EGFR mutations in adenocarcinoma

To clarify the association between the polymorphism of survivin gene and EGFR mutation, the distribution frequency of survivin (-31, +9194 and +9809) gene genotypes and EGFR mutation type in lung adenocarcinoma patients were estimated. As the results shown in Table 4, GC and GC+CC genotypes of survivin -31 were shown significantly association with EGFR mutation in lung adenocarcinoma patients.
(AOR = 3.622, 95% CI = 1.158-11.325 and AOR = 3.498, 95% CI = 1.171-10.448, respectively). Moreover, the results of Table 5 were shown that GC+CC genotypes of survivin -31 were shown slightly association with L858R mutation in lung adenocarcinoma patients (AOR = 0.5187, 95% CI = 0.935-2.242). These results indicated the polymorphism of survivin -31 genes were associated with EGFR mutation in adenocarcinoma patients.

Associations between survivin SNPs and clinicopathological characteristics of lung cancer

To revealed the association between polymorphisms of survivin gene and different clinical stage of lung cancer in different EGFR mutation of patients. As shown in Table 6, CG+GG genotype of survivin -31 was shown significantly association with clinical advanced stage in lung adenocarcinoma patients with exon 19 mutations (OR = 4.800, 95% CI = 1.305-17.658; p=0.014). These findings indicated that the polymorphisms of survivin -31 may associated with clinical advanced stage of lung cancer.

Discussion

Survivin is an apoptosis-suppressing protein and its association with many types of cancer (including lung cancer) has been well documented [30, 31, 35, 36]. However, few studies have investigated how SNP is related to EGFR mutations or prognosis in lung cancer. The present study revealed that survivin -31 polymorphism may be associated with EGFR mutations, particularly L858R mutations. Furthermore, in patients with exon 19 mutations, survivin -31 polymorphisms have an increased incidence to develop late-stage. To our best knowledge, the present study is the first reports to show a link between survivin SNP and EGFR mutations in patients with lung cancer.

Table 3. Demographics and clinical characteristics of 190 patients in lung adenocarcinoma with EGFR mutation status.

| Variable               | Wild type (N=82) n (%) | L858R (N=52) n (%) | In-frame deletion (N=49) n (%) | Others (N=7) n (%) |
|------------------------|------------------------|--------------------|-------------------------------|-------------------|
| Age                    |                        |                    |                               |                   |
| <30                    | 2 (2.4%)               | 0 (0%)             | 1 (2.0%)                      | 0 (0%)            |
| 30-39                  | 2 (2.4%)               | 0 (0%)             | 1 (2.0%)                      | 0 (0%)            |
| 40-69                  | 10 (12.2%)             | 5 (9.6%)           | 8 (16.3%)                     | 0 (0%)            |
| 50-69                  | 14 (17.1%)             | 7 (13.5%)          | 14 (28.6%)                    | 2 (28.6%)         |
| 60-69                  | 19 (23.2%)             | 13 (25.0%)         | 10 (20.4%)                    | 0 (0%)            |
| >70                    | 35 (42.7%)             | 27 (51.9%)         | 15 (30.6%)                    | 5 (71.4%)         |
| Mean ± SD              | 65.16 ± 15.06          | 68.17 ± 12.62      | 60.98 ± 13.56                 | 71.57 ± 12.04     |
| Gender                 |                        |                    |                               |                   |
| Male                   | 52 (63.4%)             | 10 (19.2%)         | 22 (44.9%)^a                  | 4 (57.1%)         |
| Female                 | 30 (36.6%)             | 42 (80.8%)         | 27 (55.1%)                    | 3 (42.9%)         |
| Cigarette smoking status |                      |                    |                               |                   |
| Never-smoker           | 35 (42.7%)             | 46 (88.5%)         | 36 (73.5%)^a                  | 4 (57.1%)         |
| Ever-smoker            | 47 (57.3%)             | 6 (11.5%)          | 13 (26.5%)                    | 3 (42.9%)         |
| PKP                   | 51.89 ± 21.46          | 40.00 ± 26.08      | 29.00 ± 17.29                 | 56.67 ± 16.07     |
| Disease stage          |                        |                    |                               |                   |
| IA                     | 8 (9.8%)               | 4 (7.7%)           | 5 (10.2%)                     | 1 (14.3%)         |
| IB                     | 6 (7.3%)               | 8 (15.4%)          | 7 (14.3%)                     | 1 (14.3%)         |
| IAII                   | 4 (4.9%)               | 3 (5.8%)           | 3 (6.1%)                      | 0 (0%)            |
| IBII                   | 0 (0%)                 | 0 (0%)             | 0 (0%)                        | 0 (0%)            |
| IIIA                   | 11 (13.4%)             | 7 (13.5%)          | 2 (4.1%)                      | 0 (0%)            |
| IIIB                   | 14 (17.1%)             | 5 (9.6%)           | 3 (6.1%)                      | 1 (14.3%)         |
| IV                     | 39 (47.6%)             | 25 (48.1%)         | 29 (59.2%)                    | 4 (57.1%)         |

^aSignificant difference compare with wild type group, p value<0.05.
^bSignificant difference compare with L858R group, p value<0.05.

Table 4. Distribution frequency of survivin genotypes of 82 EGFR wild type and 108 EGFR mutation type in lung adenocarcinoma patients.

| Variable               | Wild type (N=82) n (%) | Mutation type (N=108) (%) | OR (95% CI)    | AOR (95% CI)    |
|------------------------|------------------------|---------------------------|----------------|----------------|
| survivin -31           |                        |                           |                |                |
| GG                     | 22 (26.8%)             | 13 (12.0%)                 | 1.00           | 1.00           |
| GC                     | 39 (47.6%)             | 58 (53.7%)                 | 2.517 (1.135-5.583)^* | 3.622 (1.158-11.325)^* |
| CC                     | 21 (25.6%)             | 37 (34.3%)                 | 2.982 (1.249-7.117)^* | 3.262 (0.921-11.549) |
| GC+CC                  | 60 (73.2%)             | 95 (88.0%)                 | 2.679 (1.256-5.718)^* | 3.498 (1.171-10.448)^* |
| survivin +9194         |                        |                           |                |                |
| AA                     | 51 (62.6%)             | 54 (50.0%)                 | 1.00           | 1.00           |
| AG                     | 26 (31.7%)             | 44 (40.7%)                 | 1.598 (0.862-2.964) | 1.363 (0.550-3.376) |
| GG                     | 5 (6.1%)               | 10 (9.3%)                  | 1.889 (0.604-5.904) | 1.932 (0.348-10.743) |
| AG+GG                  | 31 (37.8%)             | 54 (50.0%)                 | 1.645 (0.917-2.951) | 1.418 (0.235-8.571) |
| survivin +9869         |                        |                           |                |                |
| TT                     | 30 (36.6%)             | 43 (39.8%)                 | 1.00           | 1.00           |
| TC                     | 38 (46.3%)             | 48 (44.4%)                 | 0.881 (0.469-1.657) | 0.561 (0.229-1.376) |
| CC                     | 14 (17.1%)             | 17 (15.7%)                 | 0.847 (0.363-1.977) | 0.631 (0.170-2.338) |
| TC+CC                  | 52 (63.4%)             | 65 (60.2%)                 | 0.872 (0.483-1.576) | 1.125 (0.321-3.944) |

The AORs with 95% CIs were estimated by multiple logistic regression models after controlling for age and gender.

*p<0.05.
High expression of survivin in the blood and tissues of patients with lung cancer is also associated with clinicopathological characteristics, including metastasis and low survival rates [26, 37-39]. Previous studies have shown that high survivin expression in the blood of lung cancer patients undergoing EGFR-TKI treatment is associated with a poor prognosis [26]. The present study also identified an association between survivin -31 polymorphism and the EGFR mutation status, suggesting that EGFR mutations may impair the effect of TKIs; that is, patients with survivin -31G/G genotypes may have higher survivin protein expression. The results were consistent with previous reports that an association between SNP of survivin and lung cancer as well as higher transcriptional activity in the C/C genotype, the latter of which may elevate survivin protein expression [31, 40].

In addition to linking the SNP of survivin -31C/G to the incidence of lung cancer, previous studies have also revealed some clinical manifestations related to survivin -31 C/G polymorphism [36, 41]. For example, Javid et al. found that survivin -31C/C in lung cancer patients was associated with a poor overall survival

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**Table 5.** The associations between the polymorphisms of survivin and the EGFR hotspot mutations in lung adenocarcinoma patients.

| Variable | Wild type (N=82) n (%) | L858R (N=52) (%) | AOR (95% CI) | Exon 19 in-frame deletion (N=49) (%) | AOR (95% CI) |
|----------|------------------------|------------------|--------------|-------------------------------------|--------------|
| survivin -31 | GG 22 (26.8%) 6 (11.5%) 1.00 | 7 (14.3%) 1.00 |
|         | GC 39 (47.6%) 26 (50.0%) 5.346 (0.906-31.537) p=0.064 | 27 (55.1%) 2.756 (0.570-13.311) p=0.207 |
|         | CC 21 (25.6%) 20 (38.5%) 4.948 (0.752-32.575) p=0.096 | 15 (30.6%) 1.633 (0.245-10.872) p=0.612 |
|         | GC+CC 60 (73.2%) 46 (88.5%) 5.187 (0.935-2.242) p=0.057 | 42 (85.7%) 2.460 (0.524-11.539) p=0.254 |
| survivin +9194 | AA 51 (62.6%) 26 (50.0%) 1.00 | 23 (46.9%) 1.00 |
|         | AG 26 (31.7%) 22 (42.3%) 1.946 (0.495-7.650) p=0.341 | 21 (42.9%) 2.458 (0.650-9.291) p=0.185 |
|         | GG 5 (6.1%) 4 (7.7%) 1.241 (0.099-15.603) p=0.867 | 5 (10.2%) 2.593 (0.205-32.738) p=0.461 |
|         | AG+GG 31 (37.8%) 26 (50.0%) 0.638 (0.047-8.653) p=0.735 | 26 (53.1%) 2.481 (0.711-8.650) p=0.154 |
| survivin +9890 | TT 30 (36.6%) 16 (30.8%) 1.00 | 24 (49.0%) 1.00 |
|         | TC 38 (46.3%) 30 (57.5%) 0.967 (0.265-3.528) p=0.960 | 16 (32.7%) 0.301 (0.087-1.042) p=0.058 |
|         | CC 14 (17.1%) 6 (11.5%) 0.312 (0.042-2.308) p=0.254 | 9 (18.4%) 0.493 (0.080-3.019) p=0.444 |
|         | TT+CC 52 (63.4%) 36 (69.2%) 0.323 (0.051-2.050) p=0.231 | 25 (51.0%) 0.339 (0.108-1.063) p=0.064 |

The AORs with 95% CIs were estimated by multiple logistic regression models after controlling for age and gender.

**Table 6.** Associations between polymorphic genotypes of survivin -31 and clinicopathologic characteristics of lung cancer.

| Variable genotypic frequencies | Clinical Stage | Stage I/A/B/ IIA/IIIB | Stage IV | OR (95% CI) | p value |
|-------------------------------|---------------|------------------------|----------|-------------|---------|
| All cases (N=360) | (N=212) | (N=148) | | | |
| survivin -31 CC | 75 (35.4%) | 38 (25.7%) | 1.00 | | |
| survivin -31 CG+GG | 137 (64.6%) | 110 (74.3%) | 1.585 (0.996-2.520) | p=0.051 |
| adenocarcinoma (N=291) | (N=160) | (N=131) | | | |
| survivin -31 CC | 56 (35.0%) | 35 (26.7%) | 1.00 | | |
| survivin -31 CG+GG | 104 (56.0%) | 96 (73.3%) | 1.477 (0.891-2.448) | p=0.129 |
| squamous cell carcinoma (N=69) | (N=52) | (N=17) | | | |
| survivin -31 CC | 19 (36.3%) | 3 (17.6%) | 1.00 | | |
| survivin -31 CG+GG | 33 (63.5%) | 14 (62.4%) | 2.687 (0.684-10.561) | p=0.147 |
| Wild type (N=82) | (N=43) | (N=39) | | | |
| survivin -31 CC | 10 (23.3%) | 11 (28.2%) | 1.00 | | |
| survivin -31 CG+GG | 33 (76.7%) | 28 (71.8%) | 0.771 (0.286-2.083) | p=0.608 |
| L858R (N=52) | (N=27) | (N=25) | | | |
| survivin -31 CC | 12 (44.4%) | 8 (32.0%) | 1.00 | | |
| survivin -31 CG+GG | 15 (55.6%) | 17 (68.0%) | 1.700 (0.548-5.275) | p=0.327 |
| In-frame deletion (N=49) | (N=20) | (N=29) | | | |
| survivin -31 CC | 10 (50.0%) | 5 (17.2%) | 1.00 | | |
| survivin -31 CG+GG | 10 (50.0%) | 24 (82.8%) | 4.800 (1.305-17.658) | p=0.014* |

*p < 0.05.
rate [41], and Rosato et al. showed that the -31 C/C genotype was related to node metastasis and patient survival [36]. Moreover, Tao et al. showed that survivin 9386 C>T polymorphisms are potential independent prognostic factors in NSCLC patients treated with platinum-based chemotherapy [42]. The present study showed that survivin -31C/C was stage-related in patients with EGFR exon 19 mutations. However, this relation was not observed in the EGFR wild type or in lung cancer patients with L858R mutations. A possible explanation is that the effect of survivin differs according to the type of EGFR mutation. For example, Okamoto et al. demonstrated that gefitinib in EGFR-mutated cells modulates cell survival by suppressing survivin expression via the PI3K-AKT signaling pathway [25]. Another possibility is that EGFR L858R and exon 19 mutations exist different oncogenic ability [43]. Although the previous study showed exon 19 to have a higher oncogenic ability compared with that of L858R [43], the role of survivin in these two distinct mutation processes requires further examination.

In conclusion, our results showed that survivin genetic variants are related to EGFR mutation in lung adenocarcinoma patients and might contribute to pathological development to NSCLC. The findings provide a hint for the genesis of EGFR mutations.

Acknowledgements

This study was supported by a research grant from Chung Shan Medical University and Cheng-Ching General Hospital (CSMU-CCH-102-001). This study was also supported by a grant (CSH-2010-C-002, CSH-2011-C-014) from Chung Shan Medical University Hospital, Taiwan.

Competing Interests

The authors declare no conflicts of interest.

References

[1] Pakkala S and Ramalingam SS. Combined inhibition of vascular endothelial growth factor and epidermal growth factor signaling in non-small-cell lung cancer therapy. Clin Lung Cancer 2009; 10 Suppl 1: S17-23.
[2] Beck M and Crino L. Advances in anti-VEGF and anti-EGFR therapy for advanced non-small cell lung cancer. Lung Cancer 2009; 63: 1-9.
[3] Costa DB, Nguyen KS, Cho BC, Sequist LV, Jackman DM, Riely GJ, Yeap BY, Halmos B, Kim JH, Janne PA, Huberhan MS, Pao W, Tenen DG, and Kobayashi S. Effects of erlotinib in EGFR-mutated non-small cell lung cancers with resistance to gefitinib. Clin Cancer Res 2008; 14: 7060-7067.
[4] Tan CS, Gilligan D and Pacey S. Treatment approaches for EGFR-inhibitor-resistant patients with non-small-cell lung cancer. Lancet Oncol 2015; 16: e472-492.
[5] Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnstone BM, and Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304: 1497-1500.
[6] Ou SH. Lung cancer in never-smokers. Does smoking history matter in the era of molecular diagnostics and targeted therapy? J Clin Pathol 2013; 66: 839-846.
[7] Yang CH. EGFR tyrosine kinase inhibitors for the treatment of NSCLC in East Asia: present and future. Lung Cancer 2008; 60 Suppl 2: S23-30.
[8] Dogan S, Shen R, Ang DC, Johnson ML, D’Angelo SP, Paik PK, Brzozowski EB, Riely GJ, Kris MG, Zakowski MF and Ladanyi M. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. Clin Cancer Res 2012; 18: 6169-6177.
[9] Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Hererra K, Ichikawa A, Cornelio G and Yang PC. A prospective, multicenter, epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIioneer). J Thorac Oncol 2014; 9: 154-162.
[10] Fazlourez M, Weerasinghe C, Nazha B, Hassan S and Atlahal JP. Epidermal growth factor receptor tyrosine kinase inhibitors in elderly patients with non-small cell lung cancer. Expert Rev Anticancer Ther 2015; 15: 1327-1336.
[11] Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Compos D, Maestro R, Martin P, Siegert T, Mok T, O’Dwyer P, Ohno S, Dezui M, Findlay B, Tu D, Johnston B, Bezkaj A, Clark G, Santabarbara P and Seymour L. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353: 123-132.
[12] Cheung CH, Huang CC, Tsai FY, Lee JY, Chang SM, Chang YC, Huang YC, Chen SH and Chang JY. Survivin - biology and potential as a therapeutic target in oncology. Onco Targets Ther 2013; 6: 1453-1462.
[13] Mohabat M, Narendran A and Riabowol K. Survivin as a preferential target in cancer therapy. Int J Mol Sci 2013; 14: 23-39.
[14] Mita AC, Mita MM, Nawrocki ST and Giles FJ. Survivin: key regulator of mitosis and apoptosis and novel target for cancer therapeutics. Clin Cancer Res 2008; 14: 5000-5005.
[15] Altieri DC. Survivin and IAP proteins in cell-death mechanisms. Biochem J 2001; 348: 189-195.
[16] Oudshoorn A, Matrougui K, Bengrinez A, Koekhoopur S and Zsazsiau M and Yousief Z. Survivin is not only a death encounter but also a survival protein for invading tumor cells. Front Biosci 2007; 12: 1260-1270.
[17] Rodell F, Sprunger T, Kaina B, Liersch T, Rodel C, Fulda S and Hehlhans S. Survivin as a prognostic/predictive marker and molecular target in cancer therapy. Curr Med Chem 2012; 19: 3679-3688.
[18] Fan CF, Xu HT, Lin XY, Yu JH and Wang EH. A multiple marker analysis of apoptosis-associated protein expression in non-small cell lung cancer in a Chinese population. Folia Histol Cytochem 2011; 49: 231-239.
[19] Huang LN, Wang DS, Chen YQ, Zhao CL, Gong BL, Jiang BA, Jia W and Hu FD. Expression of survivin and patients survival in non-small cell lung cancer: a meta-analysis of the published studies. Mol Biol Rep 2013; 40: 917-924.
[20] Wu YK, Huang CY, Yang MC, Lan CC, Lee CH, Chan EC and Chen KT. Nuclear survivin expression: a prognostic factor for the response to taxane-platinum chemotherapy in patients with advanced non-small cell lung cancer. Med Oncol 2014; 31: 239.
[21] Chen XQ, Yang S, Kang MQ, Li ZY, Lu HS and Lin YY. Survivin expression in human lung cancer and the influence of its downregulation on the biological behavior of human lung cancer cells. Exp Ther Med 2012; 3: 1010-1014.
[22] Gao Q, Yang S and Kang MQ. Impact of survivin and Bcl-2 expression in the biological behavior of non-small cell lung cancer. Mol Med Rep 2012; 5: 1409-1414.
[23] Yang CL, Liu YH, Ma YG, Xue YX, Liu DG, Ren Y, Liu XB, Li Y and Li Z. Curcumin blocks small cell lung cancer cells migration, invasion, angiogenesis, cell cycle and neoplasia through Janus kinase-STAT3 signalling pathway. PLoS One 2012; 7: e37960.
[24] Morgillo F, Woo JK, Kim ES, Hong WK and Lee HY. Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. Cancer Res 2006; 66: 10100-10111.
[25] Okamoto K, Okamoto I, Hatashita E, Kuswata K, Yamaguchi H, Kita A, Yamakawa K, Ono M and Nakagawa K. Overcoming erlotinib resistance in EGFR-mutation-positive non-small cell lung cancer cells by targeting survivin. Mol Med Oncol 2012; 11: 204-213.
[26] Shi WL, Li J, Bao QL, Wu JN, Ge LP, Zhu LR, Wang Y and Zhu WF. Survivin mRNA expression in blood as a predictor of the response to EGFR-tyrosine kinase inhibitors and prognosis in patients with non-small cell lung cancer. Med Oncol 2014; 31: 893.
[27] Liu Y, Li L, Qi H, Gao Y, Liu S and Xu C. Survivin -31G>C polymorphism and gastrointestinal tract cancer risk: a meta-analysis. PLoS One 2013; 8: e54081.
[28] Hsieh YS, Tsai CM, Yeh CB, Yang SF, Hsieh YH and Weng CJ. Survivin T9809C, an SNP located in 3'-UTR, displays a correlation with the risk and SNP-carcinogen interactions in oral cancer. J Dent Res 2015; 8: 7426-7433.
[29] Weng CJ, Hsieh YH, Chen MK, Tsai CM, Lin CW and Yang SF. Survivin SNP-carcinogen interactions in oral cancer. J Dent Res 2012; 91: 358-363.
[30] Guo G, Zhang Q, Yu Z, Li J, Ding Z, Li J and Tan W. Correlation between survivin genetic polymorphisms and lung cancer susceptibility. Int J Clin Exp Pathol 2015; 8: 7426-7430.
[31] Jiang JS, Kim KM, Kang KH, Choi JE, Lee WK, Kim CH, Kang YM, Kam S, Kim JS, Jun JE, Jung TH and Park JY. Polymorphisms in the survivin gene and the risk of lung cancer: a meta-analysis of 42 studies. Lung Cancer 2008; 60: 31-39.
[32] Yao L, Hu Y, Deng Z and Li J. Survivin -31 G/C polymorphism might contribute to colorectal cancer (CRC) risk: a meta-analysis. Int J Clin Exp Pathol 2015; 8: 15857-15861.
[33] Yang SY, Yang TY, Chen KC, Li YJ, Hu KH, Tsai CR, Chen CY, Hou CP, Hsia YJ, Chuang CY, Tsai SY, Chen KY, Huang YC, Su WC, Chen YM, Huising AC, Shen CY, Chang GC, Yang PC and Chen CJ. EGFR L858R mutation and polymorphisms of genes related to estrogen biosynthesis and metabolism in...
never-smoking female lung adenocarcinoma patients. Clin Cancer Res 2011; 17: 2149-2158.

[34] Su SC, Hsieh MJ, Liu YF, Chou YE, Lin CW and Yang SF. ADAMTS14 Gene Polymorphism and Environmental Risk in the Development of Oral Cancer. PLoS One 2016; 11: e0159585.

[35] Dai J, Jin G, Dong J, Chen Y, Xu L, Hu Z and Shen H. Prognostic significance of survivin polymorphisms on non-small cell lung cancer survival. J Thorac Oncol 2010; 5: 1748-1754.

[36] Rosato A, Menin C, Boldrin D, Dalla Santa S, Bonaldi L, Scaini MC, Del Bianco P, Zardo D, Fassan M, Cappelletto R and Fassina A. Survivin expression impacts prognostically on NSCLC but not SCLC. Lung Cancer 2013; 79: 180-186.

[37] Hu YM, Li J, Yu LC, Shi SB, Du YJ, Wu JN and Shi WL. Survivin mRNA Level in Blood Predict the Efficacy of Neoadjuvant Chemotherapy in Patients with Stage IIIA-N2 Non-Small Cell Lung Cancer. Pathol Oncol Res 2015; 21: 257-265.

[38] Kapellos G, Polonifi K, Farmakis D, Spartalis E, Tomos P, Aessopos A, Polizos A and Mantzourani M. Overexpression of survivin levels in circulation and tissue samples of lung cancer patients. Anticancer Res 2013; 33: 3475-3480.

[39] Tang XP, Li J, Yu LC, Chen YC, Shi SB, Zhu LR and Chen P. Clinical significance of survivin and VEGF mRNA detection in the cell fraction of the peripheral blood in non-small cell lung cancer patients before and after surgery. Lung Cancer 2013; 81: 273-279.

[40] Aynaci E, Coskunpinar E, Eren A, Kum O, Oltulu YM, Akkaya N, Turna A, Yavtun I and Yildiz P. Association between survivin gene promoter -31G/C and -644C/T polymorphisms and non-small cell lung cancer. Genet Mol Res 2013; 12: 3975-3982.

[41] Javid J, Mir R, Julka PK, Ray PC and Saxena A. Role of survivin re-expression in the development and progression of non-small cell lung cancer. Tumour Biol 2015; 36: 5543-5550.

[42] Tao KY, Li XX, Xu WZ, Wang Y, Zhu SM, Xie HX, Luo WH, Xu YJ and Xu XL. Prognostic role of apoptosis-related gene functional variants in advanced non-small-cell lung cancer patients treated with first-line platinum-based chemotherapy. Onco Targets Ther 2015; 8: 147-155.

[43] Greulich H, Chen TH, Feng W, Janne PA, Alvarez JV, Zappaterra M, Bulmer SE, Frank DA, Hahn WC, Sellers WR and Meyerson M. Oncogenic transformation by inhibitor-sensitive and -resistant EGFR mutants. PLoS Med 2005; 2: e313.