The Effect of P-Glycoprotein (P-gp), Nuclear Factor-Kappa B (Nf-κb), and Aldehyde Dehydrogenase-1 (ALDH-1) Expression on Metastases, Recurrence and Survival in Advanced Breast Cancer Patients

Yan Wisnu Prajoko*, Teguh Aryandono

Abstract

Objective: To investigate the level of three drug resistance proteins; P-glycoprotein 1 (P-gp), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and aldehyde dehydrogenase isoform 1 (ALDH1) expression and their relationship to metastasis, recurrence and survival in advanced breast cancer patients that received neoadjuvant chemotherapy. Methods: This study is a combination of prospective and retrospective cohort study involving one hundred and thirty one cases of advanced stage invasive breast cancer that have received neoadjuvant chemotherapy. Initial biopsy specimens (incisional biopsy or core biopsy) were taken from paraffin blocks. Immunohistochemistry (IHC) was used to detect P-gp, NF-κb, and ALDH1 expression. Prospectively analysed patients were followed for five years and evaluated for recurrence and death. Results: The expression of P-gp has no significant statistical correlation to metastases (p = 0.659), recurrence (p = 0.862) and survival (p = 0.835) in advanced stage breast cancer patients who received neoadjuvant chemotherapy. Similarly, ALDH1 was not correlated to metastases (p=0.186) and survival (p = 0.254) statistically. We found that NF-κB expression showed a significant correlation to metastases (p=0.004), recurrence (p = 0.016) and overall survival (p = 0.041) in advanced stage breast cancer patients after neoadjuvant chemotherapy. Conclusion: NF-κB expression is a potential marker that can be used to assess or to predict increasing risk of metastases, recurrence and survival in advanced stage breast cancer patients who receive neoadjuvant chemotherapy.

Keywords: Breast cancer- neoadjuvant chemotherapy- P-gp- NF-κB- ALDH1

Asian Pac J Cancer Prev, 20 (5), 1511-1518

Introduction

GLOBOCAN data issued by the International Agency for Research on Cancer World Health Organization showed that the incidence of new breast cancer in Indonesia were 48,998 cases (16.4 %) (GLOBOCAN, 2012). Breast cancer is one of the most prevalent malignancies in women; the 5-year prevalence rate was 187.7 per 100,000 populations with a mortality rate of 16.6 for every 100,000 cases. Based on the database of health research in 2013 issued by Indonesia Ministry of Health, cervical cancer and breast cancer is a disease with the highest prevalence, which amounted to 0.8 % for cervical cancer and 0.5 % for breast cancer (Kesehatan, 2013). Estimation for absolute number of breast cancer cases was 61.682. The domestic health survey by the Ministry of Health showed that the death rate for breast cancer is increasing, from 1.4% in 1972, 3.4% in 1980, 4.3% in 1986 and to 4.4% in 1992. The prevalence of locally advanced breast cancer in Indonesia is estimated to be higher than neighbouring countries. Currently, there are limited data describe the prevalence and outcome of locally advanced breast cancer. Ramli (2015) found that from all cases of local advanced stage breast cancer, 23% were operable stage IIIA and 40% were inoperable stage IIIB.

Approximately 70% of breast cancer patients failed to achieve complete pathological response after neoadjuvant chemotherapy, whereas that response is representative of long-term survival (Chollet et al., 1997; Smith et al., 2002). Patients with advanced stage breast cancer that poorly respond to chemotherapy are at higher risks of local and systemic recurrence, as well as poor long term disease-free survival rate. Non-optimal or poor response to neoadjuvant chemotherapy was postulated due to the combination of chemoresistant mechanisms. Such mechanisms include over expression of ATP binding cassette (ABC) transporter, apoptosis dysregulation, and possibly excess number of cancer stem cells (Weldon et al., 2001; Kuo,
Expression of ALDH1 was evaluated by the method of avidin-biotin-peroxidase using anti-ALDH1. To distinguish tumor cells with macrophage-positive ALDH1 and ALDH1-negative, double immunohistochemistry staining using ALDH1 and CD68 (a marker for macrophages) were used. 3 μm-thick paraffin section was incubated with antibody Concentrated Monoclonal Antibody Aldh1a1 (Biocare Medical, Concord, USA). ALDH1 positive expression was confirmed by sections of the same tissue that performed staining antibodies Monoclonal Mouse Anti-Human CD68 Clone KP1 Ready-to-Use (Dako, Glostrup, Denmark)

Statistical analysis

The Microsoft Excel for Mac 2011 was used to create a database for collected information. And statistic analysis was carried out with IBM SPSS Statistics 20. The survival data was statically analyzed using Kaplan Meier method to examine the correlation of each factor independently with survival data, by controlling confounding variables. P value <0.05 was considered as significant. A p value of <0.05 was considered to be statistically significant.

This research was carried out with reference to the principles mentioned in the Helsinki Declaration (2000) and the project was approved by The Medical And Health Research Ethics Committee (MHREC) Ministry of National Education Faculty of Medicine Gadjah Mada University Ref : KE/FK/195/EC.

Results

The average age of patients included in this study was 48.48 years old (SD 9.57), with the youngest was 27 years old and the oldest was 76 years old. The expression
of P-glycoprotein mostly was negative in this study population (66.4%). Only 33.6% of them were positive expression (Table 1).

In the positive population, 58.9% of them scores +1; only 22.6% are +3 (intense staining). Similar results were published by Campos et al., (2005). Their study on stage III breast cancer that received neoadjuvant chemotherapy showed P-glycoprotein positivity as much as 23.86%, and it was related with the worse prognostic of the disease. But higher rate of positivity was mentioned by Chintamani et al., (2005), which got as high as 52%. Of the entire study population, the majority (70.2%) expressed the NF-κB protein. Among the positive population, 63% of them include in the group with a population of cancer cells express the NF-κB more than 50%. NFκB positivity rate in this study are far greater than other studies. Such as the study by Montagut et al., (2006), which got a positive number of only 13%. This obvious difference is due to the difference of classification in the positive NFκB assessment. Only 20.3% of the study population expressed ALDH-1. Among the positive expression, as much as 13.7% of expressed <10% with weak-to-strong intensity. In the series of studies on 108 primary breast cancer patients, Tanei et al., (2009) found a proportion of 19% ALDH-1 positive expression, while 81% were negative. This result is similar to that obtained by this study.

There were 58 report of tumor recurrence (Figure 1).

Table 1. The Frequency of P-gp, NFκB, and ALDH1 Expression

|                | n = 131 | %  |
|----------------|---------|----|
| **P-gp1**      |         |    |
| Negative       | 87      | 66.4|
| +1 (<25% positive cells) | 26 | 19.8|
| +2 (25-50% positive cells) | 8 | 6.1|
| +3 (>50% positive cells) | 10 | 7.6|
| **NF-kB2**     |         |    |
| Negative       | 39      | 29.8|
| < 50% weak     | 19      | 14.5|
| < 50% moderate | 8       | 6.1|
| < 50% strong   | 7       | 5.3|
| > 50% weak     | 15      | 11.5|
| > 50% moderate | 15      | 11.5|
| > 50% strong   | 28      | 21.4|
| **ALDH13**     |         |    |
| Negative       | 107     | 81.7|
| < 10% weak     | 8       | 6.1|
| < 10% moderate | 8       | 6.1|
| < 10% strong   | 2       | 1.5|
| 10-50% weak    | 1       | 0.8|
| 10-50% moderate| 4       | 3.1|
| 10-50% strong  | 1       | 0.8|

1 P-gp, P-glycoprotein. Results of +1, +2 and +3 classified as positive expression; 2 NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells. Result other than “negative” considered as positive expression; 3 ALDH1, aldehyde dehydrogenase isofrom 1. Results other than “negative” considered as positive expression.

The most frequent recurrence sites were local recurrence (25.9%), followed by pleura (20.7%), and bone (10.3%). Only 1 patient experienced tumor recurrence in more than 1 location. Autopsies performed in the United States between 1943 and 1977 concluded that the metastatic pattern did not change within the 35-year range (Lee, 1983). The incidence of the six most common sites is the lungs, bones, lymph nodes, liver, pleura, and adrenal glands. Similar observations are also found in Europe. An observational study performed by Iqbal et al., (2010) found that the most frequent recurrence was loco regional, followed by visceral, and bone recurrence.

There was no correlation between P-gp expression with age, menopausal status, histopathological grade, lymphovascular invasion, or molecular subtype. Meanwhile NF-κB expression had strong correlation with lymphovascular invasion (p = 0.015), in which positive NF-κB expression is associated with positive LVI, whereas negative NF-κB expression is associated with negative LVI. There was small association with histopathological grade, although not significant (p = 0.094), positive NFκB expression was associated with high-grade histopathology, whereas negative NF-κB expression was associated with low and intermediate grade (Table 2).

**ALDH-1** expression correlates with age (p = 0.023), positive expression is related to young age (< 45 year old), whereas negative expression is associated with older age (> 45 year old). **ALDH-1** expression is also significantly correlated with molecular subtype (p = 0.000). The positive expression is higher in HER2 subtype, whereas the negative expression is higher in Luminal and Triple Negative subtypes. In a population of patients with negative ER, 66.3% of them showed positive NFκB expression (p = 0.311). In the population of patients with positive HER2, 76.9% showed positive NFκB expression (p = 0.477). These results are in accordance with that stated by Biswas et al., (2003) and Karin et al., (2002) that the activation of NFκB in human breast cancer is found mostly in the ER-negative subtype, specifically those that
demonstrate members of the EGF family of receptors including HER-2.

This study also found that HER2 positive expression had a tendency to express positive NFκB (76% vs 23.1%), although it was not statistically significant. These results are similar to study conducted by Montagut et al., (2006).
It is thought that HER2 might be involved in NFκB activation via the phosphotidyl inositol 3-kinase/Akt intracellular pathways (Biswas et al., 2000; Zhou et al., 2000; Pianetti et al., 2001).

Positive NFκB expression was significantly correlated with metastases, recurrence, and survival (p=0.004; p=0.16; and p=0.041) (Table 3). One of the reasons why NFκB significantly influences the metastatic processes is that metalloproteinases, urokinase-type plasminogen activator, and cytokines are upregulated by NFκB in highly metastatic, aggressive breast cancer lines (Helbig et al., 2003). It is also seen to increase motility of breast cancer cells by directly up-regulating the expression of CXCR4. Whereas ALDH1 as a prognostic marker, although statistically not significant showed the relationship with the long-term results. Where the negative expression of

P-gp, P-glycoprotein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ALDH1, aldehyde dehydrogenase isoform 1; y.o, years old; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; Ki67, marker of proliferation Ki-67

Table 2. Frequency of Other Identified Prognostic Factors Related to the Expression of P-gp, NFκB, and ALDH-1

| Prognostic factors | P-gp | NFκB | ALDH1 |
|--------------------|------|------|-------|
|                    | Positive (n=44) | Negative (n=87) | Positive (n=91) | Negative (n=40) | Positive (n=26) | Negative (n=105) |
| Age (y.o.) | | | | | | |
| ≤ 45 (young) | 13 (26.5) | 36 (73.5) | 36 (73.5) | 13 (26.5) | 15 (30.6) | 34 (69.4) |
| > 45 (old) | 31 (37.8) | 51 (62.2) | 55 (67.1) | 27 (32.9) | 11 (13.4) | 71 (86.6) |
| p=0.251 | | | p=0.557 | | p=0.023 | |
| Menopausal status | | | | | | |
| Pre (<50 y.o.) | 21 (29.2) | 51 (70.8) | 50 (69.4) | 22 (30.6) | 16 (22.2) | 56 (77.8) |
| Post (≥50 y.o.) | 23 (39.0) | 36 (61.0) | 41 (69.5) | 18 (30.5) | 10 (16.6) | 49 (83.1) |
| p=0.268 | | | | | | |
| Grade | | | | | | |
| 3 | 28 (30.1) | 65 (69.9) | 69 (74.2) | 24 (25.8) | 20 (21.5) | 73 (78.5) |
| 1 and 2 | 16 (42.1) | 22 (57.9) | 22 (57.9) | 16 (42.1) | 6 (15.8) | 32 (84.2) |
| p=0.223 | | | p=0.094 | | p=0.630 | |
| Lymphovascular invasion | | | | | | |
| Yes | 36 (36.7) | 62 (63.3) | 74 (75.5) | 24 (24.5) | 19 (19.4) | 79 (80.6) |
| No | 8 (24.2) | 25 (75.8) | 17 (51.5) | 16 (48.5) | 7 (21.2) | 26 (78.8) |
| p=0.209 | | | p=0.015 | | p=0.805 | |
| Molecular subtype | | | | | | |
| Luminal A | 14 (45.2) | 17 (54.8) | 20 (64.5) | 11 (35.5) | 7 (22.6) | 24 (77.4) |
| Luminal B | 9 (28.1) | 23 (71.9) | 26 (81.3) | 6 (18.8) | 3 (9.4) | 29 (90.6) |
| p=0.454 | | | p=0.094 | | p=0.630 | |
| HER2 Negative | 16 (32.0) | 34 (68.0) | 31 (62.0) | 19 (38.0) | 6 (12.0) | 44 (88.0) |
| HER2 Positive | 5 (27.8) | 13 (72.2) | 14 (77.8) | 4 (22.2) | 10 (55.6) | 8 (44.4) |
| p=0.000 | | | p=0.226 | | p=0.000 | |
| ER expression | | | | | | |
| Positive | 17 (40.5) | 25 (59.5) | 32 (76.2) | 10 (23.8) | 9 (21.4) | 33 (78.6) |
| Negative | 27 (30.3) | 62 (69.7) | 59 (66.3) | 30 (33.7) | 17 (19.1) | 72 (80.9) |
| p=0.322 | | | p=0.311 | | p=0.816 | |
| PR expression | | | | | | |
| Positive | 16 (33.3) | 32 (66.7) | 35 (72.9) | 13 (27.1) | 6 (12.5) | 42 (87.5) |
| Negative | 28 (33.7) | 55 (66.3) | 56 (67.5) | 27 (32.5) | 20 (24.1) | 63 (75.9) |
| p=1.000 | | | p=0.560 | | p=0.119 | |
| HER2 expression | | | | | | |
| Positive | 7 (26.9) | 19 (73.1) | 20 (76.9) | 6 (23.1) | 12 (46.2) | 14 (53.8) |
| Negative | 37 (35.2) | 68 (64.8) | 71 (67.6) | 34 (32.4) | 14 (13.3) | 91 (86.7) |
| p=0.493 | | | p=0.477 | | p=0.001 | |
| Ki67 expression | | | | | | |
| > 13% | 18 (33.3) | 36 (66.7) | 41 (75.9) | 13 (24.1) | 11 (20.4) | 43 (79.6) |
| Neg and < 13% | 26 (33.8) | 51 (66.2) | 50 (64.9) | 27 (35.1) | 15 (19.5) | 62 (80.5) |
| p=1.000 | | | p=0.247 | | p=1.000 | |
ALDH1 was found more in the group that metastases did not occur, recurrence did not occur, and also have longer survival (p=0.120; p=0.186; p=254).

Expression of P-gp has no effect on recurrence time (p = 0.86). On the other hand, expression of NF-κB has a relationship to the recurrence time (p = 0.02). Where a tumor with a positive expression has a higher recurrence rate. This study also obtained the result that the presence of intratumoral ALDH1 cancer stem cells was associated with recurrence time although statistically it was not significant (p = 0.19). It can be seen that in the first twenty months, patients with positive expression of ALDH1 showed a higher recurrence rates. A somewhat different result were delivered by Resetkova et al., (2010) they found that positive expression of ALDH1 did not correlate with disease free survival.

The P-gp expression was not related to overall survival (p = 0.84). However the expression of NFκB was significantly associated with overall survival (p = 0.04), where positive expression had a worse overall survival. The expression of ALDH1 appears to have a relationship to overall survival, although it was not statistically significant (p = 0.25). Where at least in the first forty months, the positive expression of ALDH1 showed a worse overall survival. Resetkova et al.,(2010) found different results reporting ALDH1 expression did not correlate with overall survival. However, Ginestier et al., (2007) and Neumeister et al., (2009) reported similar results showing stronger expression of ALDH1 is related with poorer long-term survival.

Discussion

This study has found no significant correlation between P-gp with recurrences, metastases, and long-term survival of advanced breast cancer patients. This finding is similar to the results reported by Pinedo and Giaccone (1995) which states that in breast cancer, even the positive expression of P-gp is more commonly found in locally advanced tumors, however the correlation has not been observed. They stated that perhaps P-gp is more a marker of tumor aggressiveness than of response to the treatment.

As postulated at the beginning that the expression of ALDH1 is related to a worse prognosis, this study seems to show the relationship between ALDH1 expression with recurrences, metastases and long-term survival, although these results were not statistically significant. Ginestier et al., (2007) in their research had shown that ALDH1 is a better marker in identifying breast cancer stem cells. Abraham et al., (2005) and Ginestier et al., (2007) have proven the existence of breast cancer stem cells and their relation to a biologically aggressive phenotype. ALDH1 positivity generally also expresses high level of ABC transporter, so it is estimated to be resistant to chemotherapy. Different results in this study can be cause by various conditions. For example by different staining methods, or the weakness arising form paraffin block production from the beginning of the preparation to the staining phase.

Several studies have been conducted to identify reliable predictive and prognostic factors to determine therapeutic response and long-term results on locally advanced breast cancer. Classical clinical-pathological parameters that have been studied, including age, tumour size, nodal status, nuclear tumour grade, hormonal receptor status, HER2 expression, Ki67 expression, etc. It is estimated that a combination of these factors in breast cancer management has a higher predictive and prognostic value. But the role of these factors in term of prognostic value, especially in locally advanced breast cancer is often vague. The prognostic value of NFκB in several types of cancer has been previously reported (Lessard et al., 2003; Fradet et al., 2004; Ross et al., 2004; Domingo-Domenech et al., 2005; Xia et al., 2014).

Our study found a significant correlation between NFκB positivity and poorer prognosis in terms of recurrences, metastases, and long-term survival. These results are in line with what was conveyed by Dolcet et al., (2005) that tumors with constitutive NFκB activation usually show increased resistance to chemotherapy, and ultimately affect long-term result. It was also reported that NFκB might induce expressions of the multidrug resistance P-glycoprotein. Some preclinical studies also have shown activation of the NFκB pathway by different chemotherapy agents, including anthracyclines and taxanes (Das and White, 1997; Bottero et al., 2001; Ho et al., 2005). This unfavourable effect also results from the activation of anti-apoptotic genes by NFκB (Wang et al., 2012). The role of NFκB expression as prognostic factor in breast cancer especially the locally advanced stage seems very promising. Hence it can be applied in patient...
management, along with other established prognostic factors. Perhaps from a therapeutic side it does not have clear clinical benefits, but its role as a new prognostic factor will help us classify patients into groups with good or worse long-term result predictions. Therefore we can plan the steps needed both sociopsychologically and medically including therapeutic planning that might use. Hopefully this research can increase our knowledge, especially in breast cancer management.

Statement conflict of Interests
None declared.

References

Abraham BK, Fritz P, McClellan M, et al (2005). Prevalence of CD44+/CD24−/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. Clin Cancer Res, 11, 1154-9.

Biswas DK, Cruz AP, Gansberger E, et al (2000). Epidermal growth factor-induced nuclear factor kappa B activation: A major pathway of cell-cycle progression in estrogen-receptor negative breast cancer cells. Proc Nail Acad Sci U S A, 97, 8542-7.

Bottero V, Rossi F, Samson M, et al (2001). Ikappa b-alpha, the NF-kappa B inhibitory subunit, interacts with ANT, the mitochondrial ATP/ADP translocator. J Biol Chem, 276, 21317-24.

Campos GP, Alvarenga M, Teixeira LC (2005). Immunohistochemical evaluation of P-Glycoprotein and its correlation to the response to neo-adjuvant chemotherapy in stage III breast carcinoma patients. Appl Cancer Res, 25, 209-14.

Chintamani, Singh JP, Mittal MK, et al (2005). Role of p-glycoprotein expression in predicting response to neoadjuvant chemotherapy in breast cancer—a prospective clinical study. World J Surg Oncol, 3, 61.

Chollet P, Charrier S, Brain E, et al (1997). Clinical and pathological response to primary chemotherapy in operable breast cancer. Eur J Cancer, 33, 862-6.

Das KC, White CW (1997). Activation of NF-kappaB by antineoplastic agents. Role of protein kinase C. J Biol Chem, 272, 14914-20.

Dolcet X, Llobet D, Pallares J, et al (2005). NF-kB in development and progression of human cancer. Virchows Arch, 446, 475-82.

Domingo-Domenech J, Mellado B, Ferrer B, et al (2005). Activation of nuclear factor-kB in human prostate carcinogenesis and association to biochemical relapse. Br J Cancer, 93, 1285-94.

Fojo AT, Ueda K, Slamon DJ, et al (1983). Breast carcinoma: pattern of metastasis at autopsy. J Clin Oncol, 1, 555-67.

Helbig G, Christopherson KW, Bhat-Nakshatri P, et al (2003). NF-kappaB promotes breast cancer cell migration and metastasis by inducing the expression of the chemokine receptor CXCR4. J Biol Chem, 278, 21631-8.

Ho RC, Hirshman MF, Li Y, et al (2005). Regulation of IkappaB kinase and NF-kappaB in contracting adult rat skeletal muscle. Am J Physiol Cell Physiol, 289, C794-801.

Iqbal J, Ginsburg O, Rochon PA, et al (2015). Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. JAMA, 313, 165-73.

Kida K, Ishikawa T, Yamada A, et al (2016). Effect of ALDH1 on prognosis and chemoresistance by breast cancer subtype. Breast Cancer Res Treat, 156, 261-9.

Kuo MT (2007). Roles of multidrug resistance genes in breast cancer chemoresistance. Adv Exp Med Biol, 608, 23-30.

Lee YT (1983). Breast carcinoma: pattern of metastasis at autopsy. J Surg Oncol, 23, 175-80.

Lessard L, Mes-Masson AM, Lamarre L, et al (2003). NF-kappa B nuclear localization and its prognostic significance in prostate cancer. BJU Int, 91, 417-20.

Montagut C, Tusquets I, Ferrer B, et al (2006). Activation of nuclear factor-kappaB is linked to resistance to neoadjuvant chemotherapy in breast cancer patients. Endocr Relat Cancer, 13, 607-16.

Neumeister V, Rimm D (2010). Is ALDH1 a good method for definition of breast cancer stem cells?. Breast Cancer Res Treat, 123, 109-11.

Pianetti S, Arsura M, Romieu-Mourre R, et al (2001). Her-2 neu overexpression induces NF-kappaB via PI3-kinase/Akt pathway involving calpain-mediated degradation of IkappaB-alpha that can be inhibited by the tumor suppressor PTEN. Oncogene, 20, 1287-99.

Pinedo HM, Giaccone G (1995). P-glycoprotein—a marker of cancer-cell behavior. N Engl J Med, 333, 1417-9.

Ramli M (2015). Update breast cancer management diagnostic and treatment. Majalah Kedokteran Andalas. Padang: Universitas Andalas.

Resetkova E, Reis-Filho JS, Jain RK, et al (2010). Prognostic impact of ALDH1 in breast cancer: a study of stem cells and tumor microenvironment. Breast Cancer Res Treat, 123, 97-108.

Romano P, Manniello A, Aresu O, et al (2009). Cell Line Data Base: structure and recent improvements towards molecular authentication of human cell lines. Nucleic Acids Res, 37, D925-D32.

Ross JS, Kallakury BVS, Sheehan CE, et al (2004). Expression of nuclear factor-xB and IkxB proteins in prostatic adenocarcinomas. correlation of nuclear factor-xB. Immun Dis Recurrence, 10, 2466-72.

Smith IC, Heys SD, Hutcheon AW, et al (2002). Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol, 20, 1456-66.

Tanei T, Morimoto K, Shimazu K, et al (2009). Association of ALDH1 in cancer-cell behavior. Jpn J Cancer Res, 101, 2261-8.

Wang CY, Mayo MW, Baldwin AS Jr (1996). TNF- and cancer therapy-induced apoptosis: potentiation by inhibition of NF-kappaB. Science, 274, 784-7.

Wang VYF, Huang W, Asagiri M, et al (2012). The transcriptional specificity of NF-xB dimers is coded within the xB DNA response elements. Cell Rep, 2, 824-39.
Weldon CB, Burow ME, Rolfe KW, et al (2001). NF-kappa B-mediated chemoresistance in breast cancer cells. *Surgery*, 130, 143-50.

Xia Y, Shen S, Verma IM (2014). NF-κB, an active player in human cancers. *Cancer Immunol Res*, 2, 823-30.

Zhou BP, Hu MC, Miller SA, et al (2000). HER-2/neu blocks tumor necrosis factor-induced apoptosis via the Akt/NF-kappaB pathway. *J Biol Chem*, 275, 8027-31.

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.