

Fas and its ligand (FasL) are known to play a crucial role in the genetically controlled mechanism of cell death, and their deregulation in cancer cells is involved in the immune escape of the tumor. The aim of this review is to analyze the current knowledge on the prognostic value of Fas/FasL in breast cancer patients. Both the results of other authors and our own experiences indicate that the lack of Fas ligand, and particularly Fas, is related to a significantly worse prognosis. It probably results from the resistance of Fas-deficient breast tumors to the mechanisms of apoptosis. On the other hand, some results suggest that the Fas/FasL-dependent mechanisms of tumor spread may be different for various target tissues. The expression of the Fas/FasL system has potential prognostic application in view of current knowledge, and consequently should be considered as an additional prognostic factor in breast cancer patients.

Key words: breast cancer, Fas, Fas ligand, prognosis.

Prognostic value of the Fas/Fas ligand system in breast cancer

Marek Bębenek¹, Danuta Duś², Joanna Koźlak²

¹1st Department of Surgical Oncology, Regional Comprehensive Cancer Center, Wrocław, Poland

²Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wrocław, Poland

Introduction

Apoptosis is a genetically controlled mechanism of cell death, regulating tissue homeostasis. Pro-apoptotic signaling is mediated by specific ligands and surface death receptors which are capable of transmitting it from an extra- to an intracellular environment and activating the execution of apoptosis [1].

Death receptors belong to the tumor necrosis factor (TNF) family, whose most important members are TNF-R1 and Fas. The ligands for these receptors form a group of related cytokines consisting, inter alia, of TNF- α , lymphotoxin (LT α), Fas-ligand (FasL) and TRAIL. These ligands function in an autocrine or paracrine manner and their binding to the respective cell membrane receptors is essential for apoptotic signaling. FasL is normally synthesized as a membrane protein, but can also be released from the cell surface by proteolytic cleavage [2, 3]. Both the Fas receptor and FasL are predominantly expressed on activated cytotoxic T and NK lymphocytes (CTLs). Binding of FasL to its receptor is reflected in the apoptosis of CTLs, consequently participating in the maintenance of immunological homeostasis. FasL expressed in some structures, such as in the testis or the anterior eye chamber, protects them from autoimmune cytotoxic lymphocyte attacks. The tumor-specific immune response, executed by CTLs, is however also the key host reaction against cancer [4].

It was revealed that the tumor expression of FasL, inducing the apoptosis of CTLs, might enable the neoplasm to evade immune destruction by these cytotoxic cells [5]. The detection of FasL and its mRNA in the variety of human malignancies with different histogenesis supports the concept of FasL-mediated immune escape of the tumor cells [6–14]. In some cases, FasL and its mRNA were detected more frequently in tumor metastases than in primary tumors [15]. Many further findings seem to confirm the hypothesis that a deregulated Fas/FasL system can result in the immune escape of the tumor [16, 17].

Resistance to apoptosis and alterations in Fas signaling were observed first in breast carcinoma cell lines [18]. Several further studies on breast cancer patients indicated that Fas/FasL status may have a significant impact on patient survival [12, 14, 19, 20]. Their results, together with the evidence obtained during experiments on other solid malignancies [21–27], suggest that the tumor levels of Fas/FasL possibly will influence the prognosis of oncological patients.

Surprisingly, recently both Fas and its ligand have gained less scientific interest. It is hardly justifiable particularly in the case of breast cancer where there is a need for new markers, enabling more precise prognosis and identification of patients who might benefit from aggressive treatment. The therapeutic decisions for breast cancer patients are still based mostly on tumor histological type and grade, its clinical stage, patient age, hormone receptor status and, recently, also on Her2-neu expression.

Consequently, the aim of this short review is to analyze the current knowledge of the prognostic value of Fas/FasL in breast cancer patients and the pos-

sibilities of clinical implementation of these molecule determinations. Both the literature data and our own experiences are considered here.

Prognostic value of Fas/FasL expression in breast cancer

Results of various authors suggest that the phenotype of Fas-deficient primary breast tumor is more aggressive and usually reflects a worse prognosis. Mottolese *et al.* [19] revealed that the disease-free survival was significantly longer in patients with Fas-positive tumors compared to the ones with Fas-negative breast cancer tissues. The aforementioned results were further confirmed by Reimer *et al.* [20] and Botti *et al.* [14], who found that the FasL : Fas ratio > 1 was related to significantly shorter disease-free survival.

The aforementioned data were further completed with the results of our studies on breast cancer patients. They have proved significant associations between the lack of Fas expression and lymph node involvement or the number of recurrences [28]. Fas expression in the primary tumor was also considerably less frequent among breast cancer patients with bone metastases compared to women without skeletal spread. Moreover, negative staining for Fas proved to be a significant predictor for survival free from bone metastases under univariate analysis [29]. Finally, the expression of Fas was significantly less frequent in breast cancer patients in whom malignant cells infiltrated through the perilymphatic fat. Simultaneously, the infiltration of paranodal fatty tissue occurred more often in cases of ductal carcinomas, larger primary tumors ($pT \geq 2$) and regional lymph node involvement ($pN \geq 1$), and shortened overall survival in breast cancer patients under univariate analysis [Bębenek, Duś, Koźlak – unpublished]. Consequently, the latter experiment also confirmed the negative prognostic value of Fas deficiency in primary tumors.

Searching through the available literature, however, we have found markedly less information on the prognostic value of Fas ligand in breast cancer patients. Our studies to date revealed that the presence of FasL is characteristic for poorly differentiated breast cancer specimens – G3 [28]. Similar results were previously described by Reimer *et al.* [20]. The role of FasL in the skeletal spread of breast cancer seems to be similar to the role of Fas. We have demonstrated that Fas ligand expression in the primary tumor was considerably less frequent among breast cancer patients with bone metastases compared to women without skeletal spread [29]. Interestingly, conversely to Fas, a similar association was not observed between the expression of FasL and the neoplastic infiltration of perilymphatic fat [30]. We have previously shown that lymph node involvement was associated with the lack of Fas in primary breast tumors, while it was independent from the occurrence of Fas ligand [28]. Consequently, the molecular background of nodal and paranodal invasion of breast cancer seems to be similar in terms of Fas/Fas ligand expression.

Studying the influence of the tumor expression of Fas ligand on the outcome of breast cancer patients, Sjöström *et al.* [12] demonstrated that among a small panel of apoptosis-related molecules FasL was the most significant predic-

tor of overall survival. That relationship, however, was not further confirmed by other authors. Also our experiences do not support the impact of Fas ligand expression on the outcome, in terms of both overall and disease-free survival [28]. Nevertheless, the lack of Fas ligand expression proved to be a significant predictor for survival free from bone metastases [29].

In conclusion, the aforementioned data indicate the considerable prognostic potential of the Fas/FasL system in breast cancer patients. Both the results of other authors and our own experiences indicate that the lack of these molecules is related to a significantly worse prognosis. It probably results from the resistance of Fas-deficient breast tumors to the mechanisms of apoptosis.

Nevertheless, still many questions dealing with the direct association between expression of these molecules and the survival of breast cancer patients need to be understood. Such a relationship was not demonstrated in all the analyses of survival published to date. Its probability is relatively high, however, in view of significant associations found between the lack of Fas/Fas ligand in primary tumors and the spread of breast cancer to various locations [28, 29]. It is very likely that studies with longer follow-up are necessary to confirm definitively the prognostic value of the molecules studied. It was proven that some factors, insignificant in the analyses of 5- or even 10-year survival, gained their prognostic value in the context of longer follow-ups of breast cancer patients [30].

Moreover, our results suggest that the Fas/FasL-dependent mechanisms of spread may be different for various target tissues [29, Bębenek, Duś, Koźlak – unpublished]. Also this hypothesis needs to be verified by further experiments.

Concluding, the expression of the Fas/Fas-ligand system has potential prognostic application in view of current knowledge and consequently it should be considered as an additional prognostic factor in breast cancer patients.

The authors declare no conflict of interest.

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Address for correspondence

Marek Bębenek MD, PhD
1st Department of Surgical Oncology
Regional Comprehensive Cancer Center
pl. Hirszfelda 12
53-413 Wrocław, Poland
tel. +48 71 368 93 00
fax +48 71 368 93 09
e-mail: bebmar@dco.com.pl

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