

Tumor Necrosis Factor alpha receptors p55 and p75 and ovarian cancer – state-of-the-art research and clinical implications

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Abstract

Tumor Necrosis Factor α acts via its two cell-surface receptors p55 and p75 and the effect depends on their activation. Receptors are proteins that dissociate from cell surface and become soluble molecules in serum blocking the natural activity of TNF α . It has been proved that this cytokine and both receptors could be overexpressed and constitutively produced by many malignant tumors, including ovarian cancer. However, little is known about the ovarian-specific role in cancer biology. Molecular and immunological research was not followed by many clinical evaluations of potential power of TNF α , p55 and p75. Some research supports previous laboratory results. It has been also suggested that especially receptors p55 and p75 could be useful in ovarian cancer detection, differentiation, staging or predicting prognosis, relapse and surgical debulking. Results are inspiring and promising, but should be followed by more well-designed research.

Key words: TNF alpha receptors, CD120a, CD120b, tumor markers, ovarian cancer.

Introduction

In spite of the development in diagnostics, 75% of all detected ovarian cancers are in more advanced stages III and IV (according to FIGO) with an obvious impact on therapy and poor prognosis. The outcome in patients with ovarian cancer remains a great cause of concern worldwide. Unfortunately the typical patient with detected ovarian cancer has advanced disease, due to unsuccessful early detection methods [1, 2]. The early stages of this neoplasm are typically asymptomatic and the research of new potential diagnostic method is needed worldwide. The dominating methods researched nowadays are ultrasound and tumor markers. The natural biology of cancer, its prognostic factors are still subject to research and are usually unpredictable. The possible reason to explain this problem is the biologic heterogeneity of ovarian cancer. [3]

Tumor Necrosis Factor- α

The Tumor Necrosis Factor alpha (TNF α) is a common mediator of apoptosis, inflammation and immune response. It is also crucial in pathways of such situations like sepsis, diabetes, malignancy, osteoporosis, sclerosis multiplex, rheumatoid arthritis [3, 4]. It is not organ- or disease-specific

cytokine, and its role in ovarian biology remains unclear. The cachectin (TNF α) exists as a trimer and is produced by activated macrophages, fibroblasts, mastocytes, some of subpopulations of T lymphocytes and NK cells. Its biological role in malignant tumors is clear, it was observed from years that cachectic patients with cancers have elevated expression of this cytokine. [3, 4] It was also proved that TNF α has a cytotoxic effect on cancer cell lines. [5, 6] On the level of the ovary it was shown that this cytokine could stimulate the normal ovary cells growth and simultaneously inhibit ovarian cancer cells [7, 8]. Parallel observation was made in pulmonary cancer [6]. However, opposite and confusing reports are found in literature, like those from Mutch et al. and Wu et al. [9, 10]

The miraculous regulators of TNF α effect

The effect of TNF α is regulated by its two receptors; receptor 1 (p55, CD120a) and receptor 2 (p75, CD120b), which are present in most of human cells. The signal is transferred into the cell via a complicated protein system to target transcription proteins: nuclear factor κ B (NF- κ B) and c-Jun. This pathway results in regulations of cell growth, death, carcinogenesis and stress response [4,11]. Many studies support the dominating role of receptor I (p55) in signal transduction, whereby receptor II (p75) plays a modulatory role, being incapable of transducing the signal alone [1, 4, 5, 11, 12]. However, it was hypothesized that both receptors could be agonists and antagonists dependent on their concentrations. [13] The role of p75 probably consists of enhancing the p55 signal and increasing ligand-receptor adhesion [1, 5, 12]. Bazzoni et al. [14] distinguish between apoptotic activity of receptor I and proliferative of receptor II. Thus the expressions and concentrations of TNF α and receptors p55 and p75 are not determining the final effects of this complex, but their internal proportions. That is why it seems to be more important for tumor biology to find out what the expressions and concentrations of TNF α receptors p55 and p75 are rather than those of TNF α alone in determining the final effects [14].

The biological activity of TNF α depends on which of its receptors is activated. The expressions of p55 and p75 differ dependent on the kind of cell and are not regulated by the ligand itself [11, 14, 15]. A higher concentration of p75 is typical of monocytes and lymphocytes whereas receptor p55 is quite typical of epithelial cells [15].

Receptors dissociate from the cell surface becoming free molecules in blood. Serum p55 and p75 interact with TNF α in the same manner as if bound to the cell surface. The significance of serum complex formation is the blocking of appropriate biological effect of TNF α by competition with cell surface receptors [3, 7, 11, 14, 16]. Both receptors

dissociate from the cell surface, but the dissociation ratio is higher for type II [11]. The significance of these interactions is still unclear and remains the subject of a few studies. Some qualitative data are not clearly followed by quantitative studies. In a few studies it has been suggested that there are changes in p55 and p75 concentrations on cell surfaces as well as serum levels in patients with benign and malignant ovarian tumors [17-21].

The Tumor Necrosis Factor alpha is overexpressed in ovarian cancer. It refers especially to serous tumors and epithelial parts that are microenvironment of different TNF α tumor concentrations [18,22]. The TNF α receptor p55 is also produced practically by all types of ovarian cancer in vitro and its tumor distribution is more constant. Usually no expression of p55 is observed in tumor infiltrating cells. Unlike p55, the type II receptor (p75) is produced in stromal cells and imitates macrophages distribution [18]. According to Naylor et al. [18] genetic expression of TNF α and its two receptors has no correlation with serum levels, some observed tendency was not statistically proven in their study.

The summary of probable and known interactions between TNF α and its two receptors in cancer pathology is drawn in Figure 1.

Too early for clinical application?

What to do with the cancer that is so rarely identified early? Is the theoretical or basic research followed successfully by clinical studies? Some authors suggested the use of biochemical methods based on estimation of CA-125 [23-25]. This marker is elevated in patients with ovarian cancer, although the mean value is strongly influenced by high values in women with malignancy of advanced stage. Thus even promising results are in fact misleading, because the percentage of early stages in published papers is usually low. [2, 26] The low value of CA-125 in early diagnosis is one of the reasons preventing it from becoming a widespread screening tool. It failed to detect early stages of cancer, but is still a reference marker being compared with new ones and is useful for follow-up. [2, 21, 23, 24, 26, 27].

Clinical evaluation of receptors p55 and p75 was rarely performed, especially in cases of ovarian cancer. Not much has been known so far. Results from not numerous studies are inconsistent and more inspiring for further research than confirming basic research.

The concentrations of soluble p55 and p75 were reported to be higher in many malignant diseases. In one of studies mean serum concentrations of p55 and p75 in melanoma patients were higher than in control groups for both receptors respectively [28]. Higher concentrations of both receptors were more typical for metastatic potential of cancer in the above mentioned study. In our previous research among

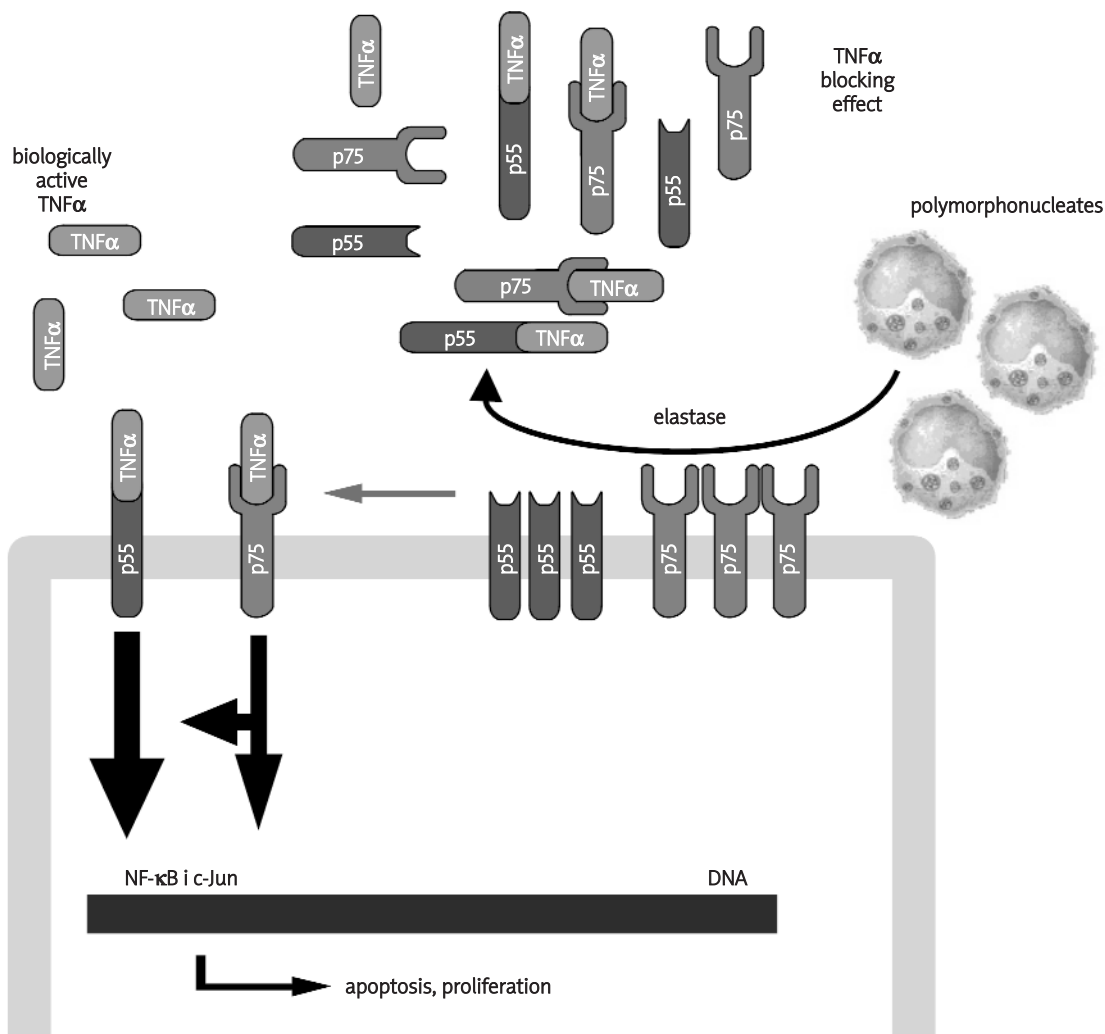


Figure 1. The pathway and interaction of TNFα and its two receptors: p55 and p75, cell surface and soluble

patients with ovarian cancer higher concentrations of p55 and p75 were observed among patients with ovarian cancer, but only in the case of receptor 1 it reached statistical significance. [20, 21] Gadducci et al. [17] report similar results to our study and additionally p55 and p75 correlated also with FIGO stage, but not with histological type, grade, CA-125 levels and possible operative cytoreduction. In our study not many correlations of p55 and p75 concentrations were observed, except a weak one between p55 and morphologic ultrasound score as well as CA-125. [20, 21] Interestingly, mean p55 concentrations preoperatively as well as CA-125 were lower in patients with possible optimal cytoreduction compared to the group, where only partial debulking or explorative laparotomy was possible. Burger et al. report the same tendency regarding CA-125 and p55, with even more precisely drawn surgical debulking status. [3] This prognostic value was not significant for p75 receptor [3, 29] In our previous study as well as those by Burger et al. no correlation with

histological type of cancer was found, but in some of other studies such dependence was reported [3, 19-21]. Onsrud et al. [19] investigated p55 and p75 concentrations in serum and ascites in patients with benign and malignant ovarian tumors. They observed higher levels in benign and highest in the malignant process, not dependent on histological type.

Summarizing the serum TNFα receptor 1 concentrations in some studies showed more relationship to clinical status (morphologic score, CA-125, sensitivity, specificity, optimal cytoreduction) than receptor 2. It supports the theory that the serum source of p55 is more likely to originate from the ovarian cancer cells. [3, 20, 21] It was reported that practically all ovarian cancer types produce p55 and its distribution in tumor is almost constant. The receptor 2 is typically produced by stromal cells [18].

An interesting observation, yet rarely researched parameter, is the estimation of p55/p75 ratio. Not many studies analyze the proportion of expression nor the peripheral concentrations ratio of p55/p75. But

additionally to our previous study, 5 other case-control studies were found in the literature. It could be reasonable to analyze them together. [3, 17-19, 21, 30] Viac et al. [28] estimated mean p55/p75 ratio in healthy controls for 0.48 and in melanoma patients much lower: 0.28. In our previous study a similar shift in the proportion of p55/p75 towards much higher concentrations of p75 resulting in lowering p55/p75 ratio was observed. [21] However, the majority of ovarian cancer patients had higher p55/p75 ratio, the mean was 0.73. Strong concentration of p55/p75 values distribution in healthy controls was observed, with the mean of 0.55 ± 0.06 [20, 21]. Similar results have been found in the literature [28, 31]. In other studies among healthy controls this ratio was not calculated, but indirectly it could be evaluated about 0.7 [32]. Naylor et al. [18] did not calculate the mean p55/p75 ratio in controls and ovarian cancer, but from his results it could be estimated to be 0.5 and 0.46 respectively. There was also a tendency in controls to have p55/p75 ratios close to the mean value and a much wider range in ovarian cancer, with lower and higher ratios. They also investigated abnormal expression of both receptors in ovarian tumors and normal ovarian tissue [18]. From the study by Grosen et al. [30] only approximate mean values of this ratio could be calculated, being 1.05 and 0.4 in different gynecologic cancers and controls respectively. Also the in vitro study of Kost et al. [5] supports the hypothesis of massive disturbances in p55/p75 ratio on the surface of ovarian cancer cells, with the values varying from 2.3 to 97. Such findings partially explain results from sera in women with ovarian neoplasm in the above mentioned studies. Also the question is, whether p55 and p75 molecules are derived from the tumor or are produced by a non specific immune response. They seem to originate from tumor because they are overexpressed in the cancerous tissue and ascitic fluid at concentrations much higher than in serum. In addition, the expression of p55 increases more than p75, as evidenced by an increase in p55 concentrations in ascites and serum, which supports the hypothesis of tumor origin [18, 19, 22].

Some studies report also the usefulness of estimation of both receptors for follow-up of clinical remission, prediction of relapse [17, 19]. The progression of the disease could be also partially predicted based on both receptors. [3] Also worth noticing is that p55 and p75 were better predictors of malignancy in ascitic fluid than CA-125 in some studies [19]. Grosen et al report even a higher value of serum p55 and p75 estimation than well known CA-125 in ovarian tumor differentiation [30]. However, these results need to be confirmed.

The interesting question is whether p55 and p75 concentrations, and especially their ratio, are influenced by other factors. And also in this case little is known. Some authors report that concentrations of p75 do not depend on the

menstrual cycle [33]. In other studies, during the monitoring of severe multiorgan traumas, including the central nervous system, the concentrations of p55 and p75 increased, but their proportion remained within values 0.45 and 0.65, except first 6 hours after trauma (maximum values 1.0), being similar to healthy controls in many studies with cancers [20, 21, 31].

In many studies the power of p55 and p75 in detecting ovarian cancer was limited, it failed to detect especially early stages. [20, 21] But this fine triple combination of rapidly varying molecules (TNF and its two receptors) could be misleading. When special indirect proportion between both receptors was introduced, clinical parameters reached much higher values. The p55/p75 ratio was not only capable of detecting malignancy in all stages of the disease, but the value was similar to well known ovarian cancer marker; CA-125. Interestingly, the power in detecting malignancy remained even in subpopulation of patients in early stage I of the disease. [20, 21] But the promising value needs to be researched again, in a well-designed study and with more patients in early stage of the disease. It could be probably reached only in a multicenter study. Further research should focus also on the peripheral ratio between p55 and p75.

Burger et al suggest even the refinement of current staging system, shifting it towards molecular staging. [3] Identification of key-point molecules that predict clinicopathological factors, outcome, prognosis, relapse etc. could also lead to explanation of the biological process involved in cancer pathology. Immunologic status would allow in future refinement in prevention, detection and therapeutic strategies to improve treatment results. But, which molecules? TNF α receptors? And what if it is a wrong way?

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