Expression Density of Receptors as a Potent Regulator of Cell Function and Property in Health and Pathology

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Abstract

The expression of cytokine receptors has a crucial role in many cellular processes. Recent studies reported that changes of receptor expression could control the action of mediators on target cells. The initiation of different signaling pathways and, therefore, specific effects on cells, depends on certain components forming the cytokine-receptor complex. These mechanisms control the immune response and affect both the course of diseases (oncological, autoimmune, inflammatory) and the effectiveness of therapy. This review describes the potential of immune mediator receptors to regulate the efficiency of cytokine activity during pathologic processes and ensure the variability of their biological effects. Our aim was to investigate the spectrum of potential roles of changes in mediator receptor expression for main classes of pathologies. For all major types of immune media-

tors (cytokines, interleukins, chemokines, growth factors, and tumor necrosis factors), it has been shown that changes in their receptor expression are associated with impaired functioning of the organism in chronic diseases.

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Introduction

The mediators of the immune system form a universal polymorphic network that controls the proliferation, differentiation, apoptosis, and functional activity of cellular elements in hematopoietic, immune, and other homeostatic systems. Cytokines, growth factors, chemokines, and their receptors are the main classes of these mediators, and they share properties including pleiotropy, synergistic and antagonistic actions, a cascade effect, and redundancy. Their effect on target cells is mediated by bind-

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ing to receptors, and the expression level of cytokine receptors has a crucial role in direction of many cellular processes [1–4]. For example, cytokine receptor activation leads to the initiation of signaling pathways that regulate a broad range of vital physiological functions, including metabolism [5, 6], inflammatory responses [7], osteogenesis [8], as well as the development and differentiation of blood and immune cells [9].

Because receptors have a significant role in mediating cytokine functions, researchers are actively studying their role under normal conditions and in various pathologies. Receptors and mediators are equally involved in promoting biological effects in target cells and the regulation of these effects can be modulated via different mechanisms such as the expression density of receptors on the cell surface and the level of soluble receptors, which affect the type and intensity of responses [1, 2]. Recent studies demonstrated that the functional response of cells to a mediator can be altered by modifying the expression of receptors or can be fundamentally different after a certain level of receptors is expressed [3]. Furthermore, the cross-activation of signaling pathways and the modulation of cytokine activity are possible when different ratios of different expressible receptors are induced [4].

There currently is a large body of disaggregated data reporting that the density of receptors on cells is associated with changes in cell proliferation and differentiation, the formation of antitumor immunity, graft rejection, and the intensity of inflammatory processes. Because these changes have a significant therapeutic potential, the aim of this review is to summarize the available data on the effect of receptor expression density for various classes of immunoregulatory mediators on the functional features and properties of cells under normal conditions and various pathologies.

Role of Changes in Receptor Expression Density in Health and Pathology

Oncology

Most of the publications reported the role of immune mediators in oncological processes. Malignant cell transformation is accompanied by alterations in the pattern of expressible receptors, including interleukin receptors. Mar et al. [10] found that the hyperexpression of IL-1R2 receptors on colonic epithelial cells resulted in cancer development. When high receptor expression persisted on colorectal cancer cells, they produced increased IL-6 and vascular endothelial growth factor (VEGF) levels, which

induced tumor cell proliferation, vascular growth, and metastatic cancer [10]. Pancreatic cancer cells can express IL-6 receptors on their surface membrane. The addition of IL-6 to medium containing pancreatic cancer cells with a high expression level of cytokine receptor increased cell invasiveness, which correlated with IL-6 concentration [11]. The expression density of IL-6 receptors on CD14+ cells from the peritoneal fluid of patients with endometriosis and healthy volunteers was evaluated recently. A high expression density of IL-6 receptors was reported in patients with endometriosis and the severity of pathology correlated with the number of receptors expressed on the cells [12].

Early studies reported that the high expression density of epidermal growth factor receptor (EGFR) on epithelial cells reduced relapse-free survival and increased mortality risk in patients with bladder cancer [13], breast cancer [14], esophageal squamous cell cancer [15], head and neck squamous cell carcinoma [16], glioma [17], stomach cancer [18], and oral squamous cell carcinoma [19] in contrast to those with a low level of receptor expression on cells. Furthermore, cell invasiveness was directly proportional to the level of EGFR expression. Similar results were obtained for patients with laryngeal squamous cell carcinoma [20], primary endometrial carcinoma [21], and laryngeal cancer [22]. In the case of primary endometrial carcinoma, Scambia et al. [21] revealed that well-differentiated tumors expressed fewer receptors than moderately or poorly differentiated tumors.

Recent studies of the expression density of EGFR in patients with colorectal adenoma and cancer showed that the receptor expression density was significantly higher in patients with adenoma and colorectal cancer compared with cells in the normal colonic mucosa. The EGFR density level correlated with the adenoma size and reached maximum values on cancer cells [23].

However, the altered expression of EGFR is not always a significant prognostic marker as demonstrated for spindle cell carcinoma of the head and neck, one type of head and neck squamous cell carcinoma [24]. The study revealed no apparent differences between patients with high and low densities of receptor expression on tumor cells in terms of tumor localization or stage, survival rate, metastatic disease, or recurrence. Therefore, EGFR levels are not always a useful prognostic factor.

Recent studies have investigated the intracellular effects in cells with altered expression levels of EGFR when they are exposed to cytokines (i.e., increased or reduced proliferative ability of cells and chemotaxis). Tini et al. [25] showed that the expression of Beclin-1 protein de-

creased autophagocytosis in cells with high EGFR expression. This, in turn, inhibited tumor cell apoptosis and enhanced proliferative activity. Glioblastoma patients with oncologic pathology and high EGFR expression on tumor cells had the worst clinical prognosis [25]. Patients with the lowest EGFR expression density on tumor cells had a more favorable survival prognosis.

The EGFR belongs to the subfamily of receptor tyrosine kinases. Binding between the cytokine and EGFR results in receptor autophosphorylation. Of note, both the high expression of conventional EGFR and its phosphorylated form (pEGFR) can be unfavorable prognostic factors for cancer patients. The hyperexpression of pEGFR on salivary gland tumor cells enhanced their migratory activity and promoted lymphogenic metastases and invasion into the lymph nodes [26].

Because of its involvement in oncogenesis, EGFR has a potential as target for anticancer therapy. Data demonstrating how the effect of various types of therapy depend on the expression density of EGF receptors have been published. High EGFR expression increases tumor resistance to radiation therapy. This was demonstrated for cervical cancer: patients with a high EGFR density on cells had either residual disease or disease recurrence after radiation therapy. Patients with low levels of EGFR had a longer progression-free survival [27]. Similar findings were also reported for patients with glioblastoma [28].

Accelerated radiotherapy with carbogen and nicotinamide (ARCON) therapy is a modification of radiation therapy involving carbogen inhalation and the administration of soluble vitamin PP (nicotinamine) during radiation therapy. Nijkamp et al. [29] demonstrated that patients with low EGFR expression showed a better response to ARCON therapy and longer survival. The exposure of tumor cells to hypoxia is thought to confer resistance to radiation therapy, while maximal DNA damage in cells was observed in the presence of oxygen. Binding of EGF to its receptor induced cell activation and stabilized a key hypoxic response protein, hypoxia-inducible factor 1 α . Therefore, the authors suggested that the beneficial outcome of ARCON therapy on low EGFR expressing tumors was related to the absence of this effect because of the low EGFR level.

The application of anti-EGFR monoclonal antibodies (cetuximab and panitumumab) to block EGFR has been used for cancer therapy. Available data on the effect of EGFR expression on cetuximab or panitumumab therapy are controversial. Shigeta et al. [30] studied the effect of cetuximab on several colorectal cancer cell lines and demonstrated that cetuximab significantly inhibited the

growth of cells with high EGFR expression, whereas cells with low EGFR density did not respond to cetuximab therapy. The opposite effect was reported for the treatment of squamous cell carcinoma of the head and neck with cetuximab and panitumumab. The strongest suppression of tumor cells was observed for cells with low EGFR expression [31]. The researchers attributed these results to the large size of the monoclonal antibody molecules: tight receptor occupation on the cell surface might hinder antibody binding because of spatial constraints.

The human EGFR (also known as HER-1) belongs to the family of human epidermal receptors, which includes HER-2, HER-3, and HER-4. According to the literature, these receptors are also expressed by some tumors, but alterations in their expression do not necessarily affect the vital activity of the cell and the overall disease prognosis [32, 33]. However, other studies demonstrated that the high expression of certain HER family receptors determined the histological type of cancer (e.g., stomach cancer) [34] and affected patient survival. Furthermore, HER-3 overexpression in stomach cancer aggravated the patients' condition and reduced their survival [34, 35]. High HER-2 expression in prostate adenocarcinoma was correlated with the serum level of prostate-specific antigen and had an important role in disease progression [36]. VEGF is a cytokine required for angiogenesis. VEGF receptor (VEGFR) is mainly expressed by vascular endothelial cells. There are 3 main subtypes of VEGFR (VEGFR-1, VEGFR-2, and VEGFR-3). Under certain conditions, other cells can express this receptor. For example, increased VEGFR-2 and VEGFR-3 expression on normal endothelial cells promoted the malignant transformation of cells and enhanced angiogenesis, thus contributing to tumor progression, while the high expression of VEGF receptor 3 also enhanced cell migration activity and myometrial invasion [37]. Other studies reported that the increased expression of VEGF receptor 1 on primary ovarian cancer cells was associated with a higher risk of disease recurrence after tumor resection [38].

The altered expression of VEGF receptor also influences the diagnosis of pathological processes, such as tumors. Hervey-Jumper et al. [39] showed that high VEGFR-1/2 expression on medulloblastoma cells resulted in gadolinium contrast enhancement during MRI. These tumors appeared brighter in MRI. For patients with low VEGFR-1/2 expressing tumor cells, the tumor appeared less bright [39]. This fact should be taken into account in cancer diagnosis.

The role of the altered expression of receptors for other growth factors has also been reported. The increased

expression of c-Met (hepatocyte growth factor receptor) on epithelial cells in nasopharyngeal carcinoma enhanced tumor cell motility by contributing to their metastasis into the cervical lymph nodes [40].

Chemokine receptors are usually expressed on immune cells; however, malignant cells in many oncologic disorders also express certain chemokine receptors, which are typically not detected in their normal analogues. The increased expression of the chemokine receptors CXCR7, CCR7, CCR8, and CXCR4 on tumor cells enhances their mobility by increasing the synthesis of intracellular actin, its polymerization, and redistribution in cells. Pseudopodia are formed as a result, which facilitate the spread and invasion of tumor cells. This mechanism is used by skin melanoma cells [41], cervical intraepithelial neoplasia cells (the precancerous lesion of cervical squamous cell carcinoma) [42], breast cancer [43], esophageal squamous cell carcinoma [44], and squamous cell carcinoma of the stomach [45], which metastasize into the lymphoid organs. Along with their effects on tumor cell morphology, chemokine receptors expressed on the membranes of cancer cells interact with their ligands to increase the functional activity of the ligands. In response, the cells produce growth factors and VEGF in particular [46], thus increasing the density of lymphatic vessels in the tumor and contributing to the lymphatic spread of cancer. Studies of changes in the expression of chemokine receptors on the cell surface of clinical specimens reported a common tendency: the high expression of chemokine receptors correlated with the severity of oncologic pathology and an increased risk of recurrence and death [46]. Patients with a high density of these receptors had a worse disease prognosis compared with those who had low or no receptor expression.

However, contrasting findings were obtained for the expression of the chemokine receptor CX3CR1 on bowel cancer cells [47]. The low expression of this receptor reduced the overall survival and increased the progression rate of patients. Furthermore, the CX3CR1 signaling pathway increased the adhesive interaction between cancer cells to prevent their spread in the organism.

Expression of TNF family receptors can also change during neoplasia. Increased death receptor 4 (DR4) and tumor necrosis factor receptor type 2 (TNFR2) expression on tumor cells in patients with ovarian carcinoma or breast cancer aggravated the disease course and promoted disease progression, leading to a decrease in overall survival and progression-free survival. Higher DR5 and first apoptosis signal receptor (FasR) levels on cancer cells increased tumor resistance to chemotherapy upon dis-

ease recurrence but did not affect treatment of the primary disease [48]. Elevated BCMA (B-cell maturation antigen) expression on chronic lymphocytic leukemia cells shortened the progression-free survival period and increased the risk of disease recurrence [49].

Signaling through the FasR (also known as apoptosis antigen 1 [Apo-1] and CD-95) is a key mechanism of tumor growth suppression. The sensitivity to CD95-mediated apoptosis is significantly reduced in many malignant cells, which has a crucial role in tumor progression, immune evasion of tumor cells, and resistance to chemotherapy. Even cells belonging to the same tumor types according to all parameters differ in FasR expression levels based on their derivation from different patients. Therefore, cellular responses to FasL depend on the cellular receptor density.

Zoi-Toli et al. [50] demonstrated that high FasR expression on cutaneous B cell lymphoma [51] and cutaneous T cell lymphoma cells was associated with reduced tumor progression and a lower risk of disease recurrence and death, which led to a more favorable disease outcome. The study focused on different densities of FasR expression on human kidney carcinoma cells and showed that the degree of tumor differentiation was inversely proportional to FasR expression: the higher the receptor density on cells, the more poorly differentiated the tumor was [52]. In contrast, in non-small cell lung cancer (NSCLC) studies, the highest level of FasR expression was observed in bronchoalveolar carcinoma, the most well-differentiated type of NSCLC [53]. The researchers also revealed that patients with low-expressing types of NSCLC had a shorter survival period and a higher cancer grade according to the TMN grading system.

Allergy and Autoimmunity

IL-31 receptor antagonists and IL-1 receptors are involved in the pathogenesis of atopic dermatitis. The expression density of IL-31RA on keratinocytes in the damaged skin of patients with atopic dermatitis was higher than that in healthy volunteers. The level of IL-31RA expression was increased significantly in patients with psoriasis, although to an extent lesser than in patients with atopic dermatitis [54]. Examination of peripheral blood cells from patients with atopic dermatitis [55] demonstrated that T and B cells were characterized by the reduced expression of IL-1R1 receptors, while the percentage of positive cells with IL-1R2 receptors was higher than in healthy volunteers. Furthermore, changes in the expression density and the percentage of monocytes and B cells expressing this receptor in a subpopulation can be

opposite. It was also demonstrated that multiple linear regression models have the strongest predictive power for the disease activity score (SCORAD) as they take into account all 3 components of the receptor-cytokine system: the levels of soluble receptors and cytokines, the percentage of positive cells, and the receptor levels. Similar trends were also shown for the expression of IL-1 receptors in patients with rheumatoid arthritis [56].

Changes in the expression level of IL-10 receptors contribute to the development and progression of autoimmune pathologies. Cui et al. [57] demonstrated that the course of systemic lupus erythematosus (SLE) was more favorable in patients whose mononuclear cells (CD4+ and CD8+ T cells) had high IL-10R expression. In this case, the IL-10/IL-10R axis suppressed the development of lupus nephritis [57]. Sellam et al. [58] demonstrated that reduced BAFF receptor expression on B cells increased disease activity in patients with SLE (evaluated using the SLEDAI score) promoting the development of extraglandular lesions in patients with primary Sjögren syndrome. Changes in BAFF-R expression may play a role in the development of thyroid disorders. In particular, high BAFF-R expression on mononuclear blood cells (mainly B cells, which have a higher receptor density) contributed to the increased infiltration of iron by these cells in patients with Hashimoto's thyroiditis (follicular infiltration) and Graves' disease (diffuse infiltration) [59].

Two types of receptors interact with TNF- α to mediate inflammatory effects. Interactions between TNF- α and TNFR1 promote cell survival and apoptosis, whereas as interactions with TNFR2 stimulate proliferation, cell survival, and the production of proinflammatory mediators (including cytokines) [60]. However, it is important to consider both the type of receptor and the density of the receptor on the target cell surface because receptor expression levels can differ between each cell subpopulation. The main subpopulations of immunocompetent cells (T cells, B cells, and monocytes) differ in terms of the expression of type I and II receptors both under normal conditions [61] and in rheumatoid arthritis [62], atopic dermatitis [63], and active pulmonary tuberculosis [64]. Variations in the percentage of cells expressing a corresponding receptor in cell subpopulations were not associated with the altered density of receptor expression. Hijdra et al. [65] demonstrated that the 3 main subpopulations of blood monocytes had different expressions of type 1 and 2 TNF- α receptors. The classical monocytes (CD14++CD16-) express low levels of TNFR1 and TNFR2, whereas non-classical monocytes (CD14+

CD16++) have a high level of type 2 receptor and a low level of type 1 receptor. In contrast, CD14++CD16+ intermediate monocytes have a higher expression of TNFR1 and intermediate TNFR2 expression. This different TNF- α receptor expression among monocytes was observed on cells from healthy donors and patients with sarcoidosis.

Van Caam et al. [66] considered changes in the density of type 1 TGF- β receptor on cartilage cells to be a risk factor for osteoarthritis: TGF- β -R1 expression can decrease with age, thus reducing the activating effect of cytokines on cartilage cells. It was also demonstrated that the migration ability of mesenchymal stem cells in the target direction, their differentiation into elastin- and actin-producing fibroblasts, and angiogenesis were reduced in neonates with a low density of platelet-derived growth factor receptor. Because these processes are important for the development of mature alveoli, bronchopulmonary dysplasia develops in children with low platelet-derived growth factor receptor expressing cells [67].

Other Pathologies

Cytokines and their receptors are involved in metabolism, which is linked to the level of receptor expression density. IL-18 participates in the regulation of lipid and glucose metabolism [68], and is dependent upon receptor expression density. In patients with HIV-associated lipodystrophy, the expression of IL-18 receptors correlated with high levels of ceramides in the skeletal muscle and with the enhanced levels of circulating triglycerides and high-density lipoproteins, resulting in the development of lipodystrophy [68].

Campbell et al. [69] reported that the IL-21 receptor was a therapeutic target for the treatment of tendinopathy. They demonstrated that tenocytes with high IL-21R expression were present in the inflammatory medium at the earliest phases of tendinopathy, which may cause tendon weakness. Interestingly, IL-21 was not detected in the medium when tenocytes were cultured. This suggests the presence of alternative IL-21R ligands. The reduced expression of IL-21R on cells also has its own sequelae.

When studying the role of IL-26 in patients with inflammatory bowel disease, the researchers assessed the expressions of IL-20R1 and IL-10R2 on normal mucosal cells and in patients with active and inactive inflammation, as well as in a culture of colonic subepithelial myofibroblasts. They found that IL-20R1 was expressed on epithelial cells and on other submucosal cells, whereas various cells, including epithelial cells and leukocytes expressed IL-10R2. The expression levels of IL-20R1 and

Fig. 1. Factors determining the type and intensity of effects of a mediator on the target cell.

IL-10R2 on cultured colonic subepithelial myofibroblasts was higher than 10R2 in normal and inflamed mucosa.

IL-33, another member of the interleukin 1 family, together with its receptor, contributes to the progression of atherosclerotic lesions in vessels because the increased expression of IL-33R on endothelial cells in the neogenic vessels of atherosclerotic plaques makes these cells less stable. Therefore, plaques containing large neoangiogenic areas are more prone to rupture. This explains the multiple symptoms observed in patients with atherosclerosis of carotid arteries, in contrast to asymptomatic (IL-33R-deficient) patients [70].

The varied expression of EGFR on pericoronal follicle cells after tooth removal might contribute to the histogenesis of various odontogenic cysts and hamartomas [71].

VEGFR may contribute to the progression of atherosclerosis. Plaque angiogenesis was stimulated in diabetic mice whose endothelial cells expressed high levels of VEGF receptor 2 in atherosclerotic plaques and where the plaque vasculature had increased permeability. This led to hemorrhage and inflammatory cell extravasation [72]. Tekabe et al. [72] reported altered VEGFR-1 expression on intraplaque macrophages. A high VEGFR-1 density on macrophages contributed to their recruitment into plaques.

Studies on the expression density of VEGFR-1/2 receptors in patients with Alzheimer's disease (AD) showed that VEGFR-1 was mostly expressed by neurons, while VEGFR-2 was expressed by neurons, endothelial cells, and astrocytes. Cerebral cortex cells from AD patients showed unchanged levels of VEGFR-2 ex-

pression when compared with health. The overall density of VEGFR-1, which is considered a negative regulator of VEGF, was lower in AD patients. VEGFR-1 was reported to play a role in microglial chemotaxis and the proliferation of cerebral vessels; however, no significant differences in the level of VEGFR1 expression in microglia were observed in AD patients compared with a control group [73].

The high density of CX3CR1 in carotid artery atherosclerotic plaques caused inflammation, increasing the risk of rupture and thrombosis. However, the low density of CX3CR1 expression is characterized by the presence of fibrosis, an indicator of plaque stability. These data indicate that evaluating the levels of CX3CR1 expression can be used to predict atherosclerotic plaque instability [74].

Chemokine receptors determine in which direction a cancer pathology will develop as well as contributing to the development of infectious diseases. Heredia et al. [75] demonstrated that the high expressions of CCR5 and CXCR4 coreceptors facilitated the entry and replication of macrophage-tropic and T cell-tropic HIV-1, respectively, in CD4+ cells. Potential mechanisms to reduce the level of CCR5 expression on lymphocytes include heterozygosis for the CCR5 $\Delta 32$ mutation [76, 77] and polymorphisms of the gene coding for chemokine receptors CCR5-2459 A/G and CCR2-64I [78].

The altered expression of TNF- α receptors also strongly affects the survival rate of tissues after transplantation. Niederkorn et al. [79] reported that corneal transplantation is the oldest, most common, and usually most successful form of solid tissue allografting. Although HLA matching is not normally performed and systemic immunosuppressive agents are not used, 90% of first-time cor-

Fig. 2. The regulation of cellular effects depends on the relationship between the soluble cytokine and the density of receptors expressed on cells. **a, b** No effect on the cell or weak signaling because one of the interaction components is missing. **c, d** Typical signaling. **e, f** Forced signaling/another type of signaling achieves the threshold binding level for a certain receptor.

neal allografting procedures are successful. The researchers performed corneal transplantation from 2 groups of deficient mice (TNFR1 or TNFR2 knockout mice) into the anterior chamber of normal mice. Grafts harvested from TNFR1 knockout mice were rejected in 53% of cases. In contrast, all the corneal grafts harvested from TNFR2 knockout mice were rejected (100%). Therefore, the absence of the type 2 TNF- α receptor increases the risk of corneal graft rejection. This also indicates that signaling through TNFR2 on donor cells promotes various immunoregulatory events that prevent the induction of alloimmunity [79].

Conclusions

When cytokines bind to their cognate receptors, the induced effects are determined by several types of interaction. The overall effect on the cell depends on changes occurring at different stages of the mediator-cell interaction (Fig. 1). The level of soluble factors produced is typically one of many parameters regulated by these interactions [80, 81].

A summary of data from published literature on the effect of the expression density of different cytokine receptors showed that altered receptor expression has a sig-

nificant role in functional cellular responses to the mediator and in the development of pathological conditions. Studies have confirmed that receptor density influences cell proliferation, apoptosis, and metabolism, which can trigger the development of autoimmune, oncologic, and dystrophic disorders.

For all the discussed classes of regulatory molecules, a change in the density of receptor expression regulates the functional activity of the receptor-expressing cells. Therefore, studying the level of receptor expression on the cell membrane is important for understanding disease pathogenesis, and altered receptor expression levels might be used as a therapeutic model for treating various disorders.

The expression density level of growth factor receptors has a significant role in the development of oncologic processes, and therefore it is important to study this with regard to cell transformation, disease course and outcome, diagnosis, and treatment. The altered expression density of chemokine receptors on cells is associated with morphological and functional changes of cells, and therefore the development of pathologic processes.

Changes in the expression level of TNF- α receptors cause different cellular responses upon exposure to specific cytokines, including altered cell proliferation intensity, secretion of mediators, and apoptosis induction [4]. In some cases, this increased or reduced receptor expression can be an additional diagnostic criterion for disease activity or to predict disease outcomes.

Cell receptors and their specific ligands are equally involved in interactions. Many soluble regulators have threshold levels for cell responsiveness to cytokines and/or altered cellular effects; thus, it is reasonable to expect that similar threshold levels also exist for receptor expression on cells (Fig. 2). The correlation between the expres-

sion density of receptors and soluble cytokine levels determines the type and intensity of cellular effects.

Therefore, the density of receptor expression on the cell surface and the level of receptors are equally involved in ligand-cell interactions and these mechanisms regulate the efficiency of cytokine activity and ensure the variability of their biological effects. Therefore, when studying changes in membrane-bound forms of receptors and cytokines, the percentage of receptor-carrying cells and the level of expressible receptors should be evaluated.

Research into the expression density of receptors is of practical importance to understand the mechanisms involved in cellular responses to altered expression levels of receptors under normal conditions and during various pathologies. These findings can be used as a therapeutic target for the prevention and treatment of various diseases.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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