



Review

Significance of Tumor-Cell Receptors in Human Cancer

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Abstract. Every tumor cell is equipped with an array of biologically active surface molecules, and several of these function as receptors for various ligands. They include MHC, or in the case of humans, HLA antigens, cytokine receptors, cell-adhesion molecules, growth factor receptors, Fas/Fas-ligand molecules and others. Their expressions are a subject to alterations, usually to the advantage of tumor growth and spread. Some appear on tumor cells *de novo*, having no counterparts on the respective normal cells. Detailed knowledge about the expression of tumor-cell receptors and their genotypes, in particular of cancerous ones, may provide information essential for the creation of tools for specific tumor immunotherapy.

Key words: HLA antigens; cytokine receptors; adhesion molecules; growth factors.

Introduction

There is a widely accepted view that malignant growth is a consequence of at least six pivotal alterations in cell physiology. These stem from various changes in cell genotype and include³⁶:

- self-sufficiency in growth signals,
- insensitivity to growth-inhibitory signals,
- evasion of programmed cell death (apoptosis),
- unlimited replicative potential,
- sustained angiogenesis,
- tissue invasion and metastasis.

Alterations of a tumor cell at the genome level may be demonstrated by the techniques of molecular genetics. Altered gene expression may, however, be detected by changes in the cell phenotype, either in the cell interior or on the cell surface. The latter comprises a large array of molecules which may be expressed in excess or may be down-regulated or even lost. Several of these serve as receptors for particular ligands. The

binding of a ligand to a receptor may result in signal transduction to the cell's genetic machinery, with a consequence to the cell's biology. Various ligands are expressed on infiltrating host cells and in the tumor stroma forming the tumor microenvironment (Fig. 1).

MHC Antigens

The discovery of the so-called tumor-associated antigens (TAA) raised hopes that at least some malignant tumors, including lung cancer, might be eliminated by virtue of tumor-specific T cells recognizing TAA on their targets via the MHC restriction pathway. Efficient anti-tumor cytotoxicity requires antigenic peptide to be appropriately presented on target cells in the MHC antigenic groove and specifically sensitized T cells⁸. Thus, one can say that MHC molecules fulfill a dual role, as presenters of antigenic peptides and as receptors for lymphocytes. The molecules which have been per-

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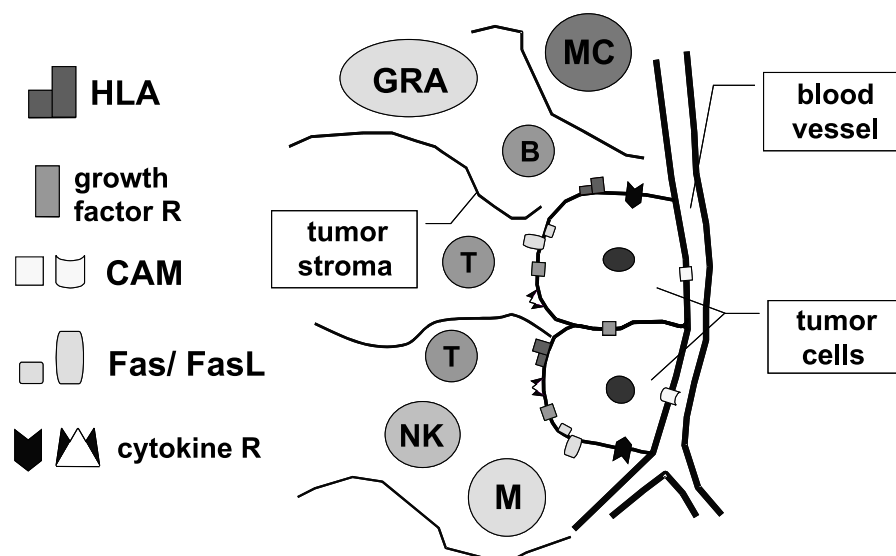


Fig. 1. Schematic view of interactions between tumor cells and tissue microenvironment *in situ*. Abbreviations: GRA – granulocytes, B – B cells, T – T cells, NK – natural killer cells, MC – mast cells, M – macrophages. Other explanations in the text

haps the most thoroughly studied are indeed the MHC or, in humans, HLA antigens. Their lack on tumor cells is advantageous to tumor growth and progression, because putative tumor antigens cannot be recognized by T lymphocytes acting via the MHC restriction pathway. HLA class I antigens may be totally lost, as is almost a rule in small-cell lung cancer and in other malignancies. This loss may be, however, selective in various tumors, limited to the disappearance of fragments of the MHC molecule, such as β 2-microglobulin or some alleles. The various forms of the MHC-linked phenotype of tumor cells resulted in the proposal by GARRIDO et al.¹³ of a classification of five major altered HLA specificities: phenotype I (total loss of HLA antigens), phenotype II (haplotype loss), III (loss of one major locus – HLA-A or -B), IV (loss of an allele), and V (combined loss). Of the five phenotypes mentioned, total loss of HLA antigens is probably the most frequent (9 to 52%), but the frequency of various altered phenotypes differs depending on the tumor histological type¹³. Moreover, the lack of HLA class I antigens may be linked with the loss of internal cell mechanisms responsible for antigen processing and presentation. CORRIAS et al.⁶ have recently shown in human neuroblastoma cells that a lack or down-regulation of HLA class I antigens on the cell surface was associated with the absence of mRNA of TAP-1 and TAP-2. These transcripts code for the important transporter proteins necessary for peptide presentation in the MHC restriction pathway.

We have tested for the presence of HLA molecules in laryngeal cancer. It was found that, in a high propor-

tion of the surgical samples of this cancer, HLA molecules could not be demonstrated at all or only on some areas of tumor. Interestingly, some cancers ($n=2$), which did not lose class I antigens, have been shown to express HLA class II molecules. Those patients with dual HLA manifestation on their tumor cells had an apparently prolonged survival time¹⁰.

Cytokine Receptors

Another group of important surface molecules on tumor cells are cytokine receptors. Several cytokines such as interleukin 2 (IL-2) and IL-6, may function as growth factors for human cancers. It has been shown that IL-2 plays such a role in carcinoma of the head and neck, while IL-6 does so in multiple myeloma and, probably, in melanoma³⁴. Other cytokines, such as IL-4, tumor necrosis factor (TNF), transforming growth factor β (TGF- β) or the interferons (IFNs), have immunoregulatory function, while some chemokines, especially the CXC group, control tumor angiogenesis²⁷. Cytokine function depends, however, on the appropriate receptors on target cells. IL-2 as well as IL-6 receptors have been demonstrated on cells of several cancers, both on the protein⁴⁴ and the molecular levels⁴². It is of interest that exogenous IL-2 can inhibit tumor growth via the tumor IL-2 receptor (IL-2R), while IL-15, which is known to bind to the same IL-2R, does not cause growth inhibition⁴².

High levels of receptors for IL-4 have been shown on human head and neck cancer cells, both *in situ* and

on 17 cancer-cell lines. The receptor involved was functional and turned out to be the IL-4R β chain, as distinct from the γ chain known to be expressed in cells of the immune system²². A chimeric protein composed of a circular permuted IL-4 and a mutated form of *Pseudomonas* exotoxin was highly cytotoxic to cancer cells, but not to normal cells expressing IL-4R, thus creating a novel approach to tumor immunotherapy²¹.

TNF- α is another cytokine of crucial importance, produced mainly by activated macrophages but also by several other cells. Its biological role is well proven in such processes as endotoxic shock, hemorrhagic necrosis of transplanted tumors, anti-viral activity, and cytotoxicity in various inflammatory and proliferative conditions. Its two receptors, p55 and p75, have been identified on the majority of cell types, apparently serving distinct functions⁴³ (see below).

We were able to show TNF- α receptors on non-small lung cancer cells. Of two TNF receptor types, p75 was much more frequently seen than p55. In pleural effusions, shed p75 molecules also predominated over p55 (in preparation). The predominance of p75 over p55 receptor is an advantage for cancer, because p55 receptor activates the intracellular cell death domain (DD), leading to cell death via apoptosis, while p75 is linked to neoangiogenesis formation by TNF- α ¹². Moreover, the p75 receptor is apparently able to act via two transcriptional pathways: nuclear factor- κ B and c-jun N-terminal kinase (JNK/SAPK)⁴⁰.

Another cytokine involved in the regulation of the cell growth and differentiation of normal squamous epithelium is TGF- β . It acts via specific TGF- β receptors and intracellular conserved signaling molecules (Smads). It has been demonstrated that type II receptor (TGF- β -IIR) expression decreases in squamous cell carcinoma as the tumor become less differentiated and more aggressive. Moreover, one of the Smad molecules, the phosphorylated form of Smad 2-P, was found to be lost in 70% of tumors. These data suggest major alterations in the TGF- β -dependent cell-signaling pathway, apparently negatively associated with tumor biology²⁸.

Cell Adhesion Molecules

Cell adhesion molecules (CAMs) comprise a vast array of cell receptors responsible for cell-cell and cell-matrix interactions. They are divided into at least five families, based on their structures and functions. These include integrins, selectins, cadherins, the immunoglobulin superfamily, and the CD44 group. Their role in

physiology has been extensively covered in several review articles^{17, 41}. Suffice to say that they are critical in the development of morphogenesis, preservation of tissue integrity, cell movement, and in cell-cell recognition. So it is obvious that, in tumor growth, genetic aberrations of tumor cells also have their reflection in the CAM phenotype^{1, 31}. For example, strict cohesion of squamous epithelium depends on several CAMs, but E-cadherins, calcium ion-dependent molecules, are probably the most important for epithelium integrity. In non-small-cell lung carcinoma, E-cadherins are frequently lost, thus facilitating tumor cell spreading into the extracellular matrix¹⁴.

VLA α_{1-6} / β_1 integrins present on activated lymphocytes react with such ligands as the various matrix proteins, such as laminin, collagen and fibronectin. Their expression on tumor cells is quite heterogeneous but usually distinct and/or down-regulated as compared with the respective normal epithelium^{25, 30}. This was also our experience when we tested frozen lung cancer sections for anti-VLA monoclonal antibodies⁴⁸.

The immunoglobulin superfamily CAMs include such items as vascular CAM (VCAM), intercellular CAM (ICAM)-1-3, Mel-CAM, neural CAM (NCAM) and CEA. VCAM and Mel-CAM were shown on melanoma cells, but acting in a reciprocal way. VCAM loss on a tumor cell appears to favor tumor progression and metastasis, while Mel-CAM expression does the same^{20, 23}.

The NCAM exists in at least three isoforms of 120, 140 and 180 kDa. They are often present on the cells of several cancers, such as small cell lung carcinoma (SCLC), multiple myeloma, renal carcinoma, rhabdomyosarcoma and others^{33, 46}. The reappearance of these molecules on tumor cells derived from the normal counterpart NCAM-negative suggests that NCAM expression confers an advantage for tumor growth. It has been proposed that the significant content of polymerized sialic acid bound to some isoforms of NCAM enables reduced homophilic interactions and creates a carbohydrate barrier that decreases other adhesive interactions, thus facilitating tumor spread¹⁹. This, however, may not always be the case, because we have shown that, in thyroid carcinoma, CD56/NCAM expression is negligible in spite of an overt, clear-cut reaction on follicular epithelial cells of normal or hyperactive thyroid⁴⁷.

The ICAM-1 has been shown to be expressed on several cancer cells, including melanoma, lung and hepatocellular carcinoma. In the latter, increased ICAM-1 VCAM expression was found to support adhesion of tumor-infiltrating lymphocytes to the tumor endothe-

lium⁴⁵. We have seen frequent expression of ICAM-1 in squamous-cell lung carcinoma, but the significance of this remains unknown.

The family of CD44 CAM consists of several isoforms or variants formed by alternative gene splicing¹⁶. CD44 is the main extracellular receptor for hyaluronic acid. Aberrant expression of CD44 variants, in particular of v6, has been found to be associated with poor prognosis³⁷. We have tested CD44 variant expression in non-small-cell lung cancer. It was found that in squamous-cell carcinoma there is an increased expression of v6 and v5, but these variants are also expressed in normal bronchial epithelium. In contrast, v7/8 variants seen in squamous-cell carcinoma could not be demonstrated in normal epithelium. In a large-cell anaplastic carcinoma, v10 predominated, being also absent on normal cells. Overexpression of these variants could not, however, be linked to the presence of metastases, at least in the cases of lung cancer tested²⁶.

Another CAM found to be linked with squamous cell carcinoma (SCC) of the lung is the epithelial glycoprotein 40 (EGP40), known as Ep-CAM or 17-1A antigen. It is an epithelium-specific ICAM expressed on basolateral surface of most epithelia. It was found to be overexpressed in a poorly differentiated SCC. Moreover, its expression rose in parallel to the involvement of regional lymph nodes and to the increasing of TNM stages³².

Growth Factor Receptors

Growth factor receptors on cancer cells are essential for tumor survival and growth⁹. Epidermal growth factor (EGF) and HER2-neu are members of the erbB gene family and encode for transmembrane receptor-type tyrosine-protein kinases. EGF receptor (EGFR) has two ligands, EGF and TGF- α . The binding of EGFR to these two ligands results in the transmission of growth stimulatory signals. EGFR and HER2-neu protein expression was demonstrated in several cancers, including lung tumors, and its prognostic importance was unequivocal. In a recent study, mRNA expression of these two receptors was tested by quantitative, real time PCR. Messenger RNA of both was found in 100% of cases, but high expression and EGFR/HER2-neu co-expression was significant as an unfavorable prognostic factor⁵.

In non-small-cell lung cancer, membranous expression of EGFR was found to be co-expressed in a significant proportion of cases (22%) with matrix metalloproteinase 9 (MMP-9), the enzyme that digests type IV

collagen in basement membranes. This association was shown to confer a poor prognosis⁷.

Insulin-like growth factor receptor I (IGF-IR) has been found to be highly expressed on the cells of several malignant tumors, both human and rodent. IGF-IR belongs to the family of transmembrane tyrosine kinase receptors and its expression is absolutely required for the establishment and maintenance of the transformed phenotype, both *in vivo* and *in vitro*.

Its ability to protect tumor cells from apoptosis raised hopes that receptor antagonists may induce apoptosis and, thus, could be used in cancer-specific therapy trials^{3, 35}.

Another example is the tyrosine kinase receptor c-Met together with ligand hepatocyte growth factor/scatter factor (HGF/SF). This is a paracrine cellular signaling mechanism, in physiological terms operating predominantly in cells of mesenchymal origin²⁴. Its overexpression has, however, been demonstrated in various malignant epithelial tumors, apparently with signs of progression^{2, 11}.

Some overt genetic abnormalities of cancer cells may result in receptor overexpression. A good example in lung cancer is the chromosome 19 translocation with an overexpression of Notch 3. Notch genes encode a family of conserved receptors involved in various biological processes such as differentiation, proliferation and apoptosis. The significance of Notch 3 expression in lung cancer awaits clarification⁹.

Also worthy of mention are the Grb7-family adaptor-protein molecules, consisting of at least three Grb7, Grb10 and Grb14 proteins and their several splicing variants. Although mostly localized in cell cytoplasm, they have also been traced on plasma membrane, especially in focal contacts. Their function is manifold, including mediating the coupling of multiple cell-surface receptors to downstream signaling pathways in the regulation of various cell activities. Thus, Grb7 may regulate cell proliferation, cell migration, apoptosis and even tumor progression. There is growing interest in the precise mechanisms governing these molecules, apparently strongly linked to cell-surface receptors¹⁵.

The Fas-Fas Ligand System

An important pair of tumor-cell receptors are the Fas-FasL molecules. It is well known that binding of FasL to Fas results in the activation of the death domain, leading to cell apoptosis. Activated T lymphocytes express FasL and, if they encounter Fas-expressing cells, the latter are killed. In cancer, tumor cells may

hide their Fas in the cytoplasm and express FasL instead. This leads to a reversed pathway: FasL on tumor cells reacts with Fas-expressing T lymphocytes, which results in the apoptosis of the tumor-infiltrating lymphocytes. Alternatively, tumor cells may shed their FasL, which may then bind to Fas on the lymphocyte surface and cause apoptotic death of the latter. This explains why in advanced cancers TIL are usually scarce or absent^{4, 29}. We were able to confirm this phenomenon in the microenvironment of malignant pleural effusions³⁹.

Concluding Remarks

Finally, the question remains of what the future holds for the research of tumor cell receptors. In the September issue of *Trends of Immunology* (2001), J. SCHULTZE and R. VONDERHEIDE provided one answer³⁸. They put forward the term “reverse immunology”, paving the way from cancer genomics to cancer immunotherapy. Their idea is based on the epitope deduction of antigens (or receptors) overexpressed on cancer cells by gene expression profiling. The latter may be done by microarray analysis or other novel techniques. Immunogenic epitopes may be predicted on the basis of HLA-binding motifs. Only genes previously shown to be involved in carcinogenesis are tested in detail. These epitopes are scrupulously tested for immunogenicity, MHC binding peptide processing, induction of T cell response and T cell cytotoxic function in experimental models and normal donors. Novel techniques at the single-cell level may be used here, such as ELISPOT and tetramer technology. Finally, fully characterized, recombinant tumor antigens are to be used in clinical trials as immunotherapeutic agents.

It remains to be seen whether this novel approach will provide some positive solutions to the management of cancer patients.

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