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Immunoediting, Immunosurveillance, Tumor-induced Immunosuppression and Immunoresistance, Immunomodulation, Immunotherapy, and Immunonutrition in Personalized and Precision Cancer Medicine

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Additional information is available at the end of the chapter

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Abstract

Cancer immunoediting is composed of three phases: elimination, equilibrium, and escape. Tumor cells, which successfully navigate these phases, are capable of evading destruction by the immunity system of the host. Furthermore, there are different types of nonimmune surveillance against tumors, including genetic surveillance, which is based on DNA repair and checkpoint control, intracellular surveillance related to apoptosis or type I PCD, intercellular surveillance linked to the tumor microenvironment, and epigenetic surveillance related to the structure of chromatin, and specifically the stringency of imprinting. Circumventing immune destruction is one of the hallmarks of cancer pathogenesis, in addition to evading growth suppressors, deregulating cellular energetics, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, sustaining proliferative signaling, and resisting cell death, which may lead to the uncontrollable promotion of tumor burden at the expense of the immune system. Although immunoediting may eliminate tumor cells with alterations in their antigenic epitope profile, many immunoresistant variants escape from the immune system of the host by various immunosuppressive molecular and cellular mechanisms. There are many immunomodulatory effects of targeted therapies that can circumvent tumor-mediated immunosuppression, improving the effector T-cell function, which enhances eradication of targeted tumors. Another even more efficient antitumor strategy consists of combining targeted therapies with immunotherapies, which exert many antitumor synergies. The subsequent complex interplay of targeted anticancer agents and immunotherapy may sensitize tumor cells to immune-mediated eradication with long-lasting immunotherapeutic effects, which may inhibit induction of tumor dormancy. These combinatorial immunotherapies with targeted therapies can be used as neoadju-

vants and adjuvant treatments with conventional anticancer strategies, such as surgical debulking, radiation therapy, and chemotherapy. In conventional anticancer treatment, the chemotherapeutic-induced immunosuppression inhibits the anticancer efficiency of cell therapies, which are based on activated lymphocytes for eradication of tumor cells, enhancing susceptibility to infections. The majority of conventional chemotherapeutic agents interfere with hematopoiesis and subsequently with the immune system, affecting the surveillance of cancer cells leading to the promotion of tumor development and growth. Furthermore, cancer surgery causes tremendous alterations in the neuroendocrine, metabolic, and immune systems constituting the stress response, which may lead to infection and cancer recurrence. Generally by using an integrative medicine immunotherapeutic approach, where alternative medicine practice which follows a multitargeted and bidirectional regulation may compensate for deficiencies of conventional orthodox western medicine, which is characterized by specificity, we may achieve a synergistic effect concerning circumvention of tumor-induced immunosuppression and enhancement of antitumor immunomodulation followed by minimization or elimination of side effects, prolonging the survival rate of advanced stage and metastatic cancer patients promoting their quality of life. The key is to treat each cancer patient under a personalized evidence-based medicine approach, which must rely on clinomics, including transcriptomics, genomics, immunomics, lipidomics, glycomics, proteomics, metabolomics, nutrigenomics, and mainly epigenomics whose alterations in their noncoding RNA genes are reversible especially with immunonutrition. The precise immunotherapeutic approach against cancer may act synergistically with conventional anticancer therapies, such as surgery, chemotherapy, and radiotherapy combined with therapies based on molecular targeting, which are tailored for each patient on a pharmacogenomic basis, and they can be combined with nanomedicine for specific molecular targeting and circumvention of biological milieu interactions, which may enhance tremendously therapeutic efficacy with simultaneous reduction of systemic toxicity.

Keywords: Immunosurveillance, immunoediting, tumor-induced immunosuppression, immunoresistance, immunomodulation, immunotherapy, immunonutrition, personalized or precision cancer medicine, evidence-based medicine, omics

1. Introduction

The strategies to fight cancer are composed of mechanisms including surgery since 1600 BC, physics including radiotherapy since 1896, chemistry including chemotherapy since 1942, and biology including immunotherapy since 1976. Although immunotherapy has a long history that has been evaluated for more than a century, only recently has it entered a renaissance phase with anticancer biological agents, including the first monoclonal antibody approved in 1997, interleukin-2 (IL-2) cytokine approved in 1998, the first cellular immunotherapy as therapeutic vaccine approved in 2010, and the first checkpoint inhibitor approved in 2011, which has been succeeded by many more approved immunotherapeutic agents [1]. The cancer immunosurveillance hypothesis proposed by Ehrlich in 1909, modified by Burnet and Thomas in 1957, refers to the immunological resistance of the host against cancer development.

2. Immunoediting and immunosurveillance

The current term is cancer immunoediting, which is composed of three phases: elimination, equilibrium, and escape. Tumor cells, which successfully navigate these phases, are capable of evading destruction by the immunity system of the host [2]. Generally, the main component of the defensive army of the host's immune system for fighting tumors is composed of cytotoxic T cells (CTLs).

The elimination phase is a process, where the immune system components recognize transformed cells, eliminating them with the use of the innate and adaptive immune system [3]. Elimination consists of four phases, where the first phase of elimination initiates the antitumor immune response, after the cells of the innate immune system have detected a growing tumor mass, which has caused damage to the local tissue after it has been through stromal remodeling. This induces inflammatory signals, which recruit into the tumor-site cells of the innate immune system, such as macrophages, dendritic cells, and infiltrating lymphocytes such as natural killer cells and natural killer T cells that release interferon-gamma (IFN- γ). The second phase of elimination involving IFN- γ induces immunogenic tumor cell death (ITCD), and it activates the release of chemokines, such as CXCL9, CXCL10, and CXCL11, which inhibit angiogenesis inducing immunogenic necrotic tumor cell death, whose apoptotic bodies are phagocytosed by dendritic cells in the draining lymph nodes, as a bystander killing effect (BKE). The subsequent inflammation releases cytokines and chemokines, which attract additional immune cells. During the third phase of elimination, the reciprocal release of cytokines IL-12 and IFN-gamma transactivates macrophages and natural killer cells, expanding tumor cell death by apoptosis or PCD type I and releasing reactive oxygen and nitrogen intermediates. Tumor-specific dendritic cells in the draining lymph nodes activate the differentiation of Th1 cells, which mediate the production of killer T cells or CD8⁺ T cells. In the fourth phase of elimination, tumor-specific cytolytic T lymphocytes CD8⁺ and CD4⁺ T cells infiltrate the tumor site after recognition of tumor-specific or tumor-associated antigens, such as MHC class I and class II molecules, which in synergy with B cells that produce antibodies, such as IgG, IgA, IgM, IgD, and IgE, facilitate innate and adaptive immune mechanisms, which mediate release cytokines leading to immunogenic tumor cell death. The cancer cells that are not eradicated by the elimination phases of the immune system proceed to the equilibrium phase, where IFN-gamma and lymphocytes prevent expansion of tumor cells that are genetically unstable and mutate rapidly. All the tumor cell variants, which have evaded immune pressure due to acquired resistance to the elimination phases where the balance between the immune response and the tumor cells is driven toward tumor growth that expands in an uncontrolled manner with nonimmunogenic transformed cells, may lead to malignancies by entering the escape phase directly [4–9].

Furthermore, there are different types of nonimmune surveillance against tumors, including genetic surveillance, which is based on DNA repair and checkpoint control, intracellular surveillance related to apoptosis or type I PCD, intercellular surveillance linked to the tumor microenvironment, and epigenetic surveillance related to the structure of chromatin and specifically the stringency of imprinting [10–13].

Circumventing immune destruction is one of the hallmarks of cancer pathogenesis in addition to evading growth suppressors, deregulating cellular energetics, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, sustaining proliferative signaling, and resisting cell death, which may lead to the uncontrollable promotion of tumor burden at the expense of the immune system [14].

3. Tumor-induced immunosuppression and immunoresistance

Although immunoediting may eliminate tumor cells with alterations in their antigenic epitope profile, many immunoresistant variants escape from the immune system of the host by the following immunosuppressive molecular and cellular mechanisms [15]. Not the immunoeffectors but only the immunosuppressive regulators are supported by the heterogeneous tumor microenvironment, which contains tumor cells, extracellular matrix (ECM) cells, local bone marrow-derived stromal progenitor cells, pericytes, endothelial cells, proteins, matrix degrading enzymes, chemokines, cellular factors, immune cells, tumor-associated fibroblasts, and angiogenic cells, which may cause desmoplasia after stromal cell infiltration and ECM deposition [16–18].

Tumors escape eradication from the immune system by mechanisms of the first category, which consists of the development of tumor immunoresistance, including the promotion of oncogenicity of tumor stem cells that causes resistance to conventional anticancer treatments and immune responses of the host due to tumor dormancy that cause tumor relapse by self-renewal, continuous ability of proliferation, incomplete differentiation, and production of immunosuppressive factors causing immunoresistance due to inhibition of apoptosis or type I PCD [19].

Another mechanism of tumor immunoresistance is the loss of abnormal surface antigens on the tumoral plasma membrane due to mutations and immunoescape of epitope loss tumor variants, which occurs due to the genetic instability of tumors, leading to continuous alterations of their surface molecules, hiding their antigenic profile by losing their epitope, especially after they sense the presence of cytotoxic T lymphocytes (CTL) in the tumor microenvironment. Thus, the immune system eradicates only the tumor cells that express the specific epitope, circumventing invisible epitope-negative tumor cells that become extremely resistant to CTL elimination [20].

One more immunoresistant mechanism exerted by the tumor cells is the lack of susceptibility to immune effector cells, such as natural killer cells (NK), cytotoxic T lymphocytes (CTL), macrophages, and dendritic cells (DC), which promote antibody-induced cytotoxicity, phagocytosis, or vaccine effects in cancer immunotherapy [21].

The second category of tumor immunoescape mechanisms consists of the interference with the antitumor-induced immune responses, such as reduced expression of costimulatory molecules on tumor cells or antigen presenting cells (APCs). This downregulation of costimulatory molecules on tumor cells or professional APC may inactivate or eliminate TAA-specific

CTLs, put in an immature state the dendritic cells conditioned by the tumor cells, and inactivate T cells leading to tumor tolerance by circumventing productive immune responses against the tumor cells [22]. Also, the tumor for escaping the immune system of the host alters the T-cell receptor (TCR) on the tumor infiltrating lymphocytes (TIL), especially in cases with advanced cancer, leading to reduced mediation of tumor cytotoxicity and decreased production of Th1-type cytokines [23–25].

The next tumor immunoescape mechanism of this category consists of death receptor/ligand signaling and tumor-induced counterattack on immune cells that induces apoptosis or type I PCD, in the majority of circulating CD8⁺ effector T cells in cancer patients, due to the overexpression of Fas (CD95) receptor on the plasma membrane of activated T cells cross-linked by FasL, which is overexpressed on tumor cells [26]. The tumor cells release immunosuppressive factors, such as PGE₂, which downregulates Jak3, blocking the IL-2R downstream signaling pathway that downregulates the prosurvival members of the oncogenic bcl-2 family, leading to a defective signaling which inactivates T cells with subsequent circumvention of tumor cells [27].

Another immunosuppressive mechanism of this category consists of dendritic cell (DC) dysfunction in tumor-associated antigen (TAA) cross presentation to T cells, which leads to a deficient immune response against tumor cells, which may deplete dendritic cells (DCs) by inhibiting the induction of TAA-specific immunity that consists of cytokines and chemokines, such as interleukins (IL-1, IL-12, IL-15, IL-18, and IL-23), interferons, and costimulatory molecules, which are required as growth factors, and signals for T-cell proliferation, differentiation, and memory development [28–30]. The tumor cells may inhibit the maturation of dendritic cells (DCs) by utilizing VEGF and block their differentiation with exosomes. Also, tumor-associated gangliosides (TAG) may downregulate proteasomal constituents of antigen processing machinery (APM) of dendritic cells (DCs) [31–34]. Furthermore, there is another tumor-induced immunosuppressive mechanism consisting of induction of apoptosis or type I PCD of dendritic cells (DCs) in the tumor microenvironment (TME), leading to their elimination by the downregulation of antiapoptotic oncogene bcl-2, the production of nitric-oxide (NO), which downregulates cellular inhibitors of apoptotic proteins (cIAPs or cFLIP), the release of ceramide, which blocks PI3K-mediated survival signals, and alterations in intrinsic apoptotic pathways [35].

One more tumor-induced immunosuppressive category consists of insufficient function of effector cells in the tumor microenvironment (TEM). Its first mechanism consists of suppression of T-cell immune responses by regulatory T cells (Treg), such as CD4⁺CD25^{high}FOXP3⁺, which accumulate in tumors, and in the peripheral circulation of cancer patients [36]. They downregulate the immune response of the effector T cells by releasing TGF- β 1 and IL-10 and involve the Fas/FasL and pathways linked to granzyme/perforin, and enzymatic ATP degradation to adenosine exerting immunosuppressive effects, which create tumor resistance [37,38]. The second mechanism of this immunosuppressive category consists of suppression of immune cells by bone marrow myeloid-derived immature suppressor cells (MDSC), such as CD13⁺, CD33⁺, and CD34⁺, which are located in the peripheral circulation of cancer patients, and they are recruited to the tumors after they release soluble immunosuppressive factors,

such as PGE₂, IL-6, GM-CSF, IL-10, VEGF, and TGF- β 1, which produce the arginase-1 enzyme that metabolizes L-arginine, activate iNOS, and control the tumor release of indoleamine-2,3-dioxygenase (IDO), which catabolizes the essential for the differentiation of T-cell amino acid tryptophan, leading to the immunosuppression of T-cell responses that promotes the survival of tumor cells [39–41]. The third immunosuppressive mechanism of this third category consists of tumor-derived microvesicles (MV) or exosomes, which express TAA, HLA class I molecules, and death ligands, which exert their immunosuppressive action by the induction of apoptosis or type I PCD in activated CD8⁺ effector T cells, eradicating their antitumor action. Also, these tumor-derived exosomes exert an additional immunosuppressive action by blocking the differentiation of monocytes to dendritic cells. Subsequently, the monocytes are transformed by the tumor-induced exosomes (MV) into CD14-negative HLA-DR low TGF- β ⁺ myeloid suppressor cells (MSC), blocking the differentiation of immune cells, which inactivates their antitumor properties by releasing TGF- β , downregulating HLA class II molecules, and inhibiting the proliferation of lymphocytes [42].

The fourth mechanism of this immunosuppressive mechanism consists of induction of apoptosis or type I PCD in effector T cells in the tumor and its periphery. Tumor cells may cause apoptotic DNA fragmentation in a proportion of activated CD8⁺ T lymphocytes and their effector subpopulations, such as CD8⁺CD28[–] and CD8⁺CD45RO⁺CD27[–], in the tumor site, and the peripheral circulation of cancer patients may lead to tumor progression due to apoptotic death of effector T-cell functions, which compromises significantly the antitumor immune responses [43–46].

The last tumor-induced immunosuppressive category consists of insufficiency in tumor recognition signals consisting of four mechanisms. The first one consists of the downregulation of expression of HLA molecules on the surface of tumor cells. As the tumor progresses, it downregulates all HLA class I allospecificities, HLA-A, HLA-B, and HLA-C loci [47,48]. The tumor cells may cause alterations in the expression of the APM components and defects in the β 2-microglobulin, and HLA class I heavy chain synthesis due to the deregulation of mechanisms involving the expression of HLA class I antigen and epigenetic alterations in the HLA class I heavy chain loci, creating resistance to adoptive T-cell-based immunotherapy due to defects into HLA class I which circumvents immune recognition, leading to tumor progression that reduces significantly survival rates of cancer patients [49]. The second mechanism consists of the downregulation of antigen processing machinery (APM) components in tumor cells or antigen presenting cells (APCs) that affect all the peptides, which are presented by HLA class I molecules to T cells enhancing tumor resistance to CTL lysis. The downregulation of total loss of expression of the HLA class I/peptide complexes circumvents the recognition and subsequent destruction of tumor cells by CTL, significantly reducing the disease-free interval and survival rate of cancer patients. The third mechanism consists of the suppression of natural killer cells (NK) in the tumor microenvironment (TME). The downregulation of the cytolytic activity against tumor cells is mediated by the action of inhibitory receptors, such as ILT2/LIRI, CD94/NKG2A, and KIR, which blocks lysis of cells expressing normal HLA class I [50]. The NK cells respond spontaneously to cytokines by expressing IL2R $\beta\gamma$, such as IFN- α , IFN- γ , IL-2, and IL-15. Upon activation, NK cells release TNF- α and IFN- γ for eradicating tumor cells. They

also interact with dendritic cells (DCs) for exerting synergistic apoptotic cell death in tumor cells [51]. However, tumor cells release TGF- β 1, which downregulates the expression of NKG2D on NK cells impairing their antitumor activity, especially in advanced stages [52]. Thus, tumors may escape the cytolytic activity of NK cells by the inhibition of interactions between receptors and ligands, the downregulation of tumoral ligands MICA or MICB, the eradication of activated NK cells mediated by overexpression of tumoral death-ligands, and the suppression of interactions between NKs and DCs in the tumor microenvironment (TME) promoting tumor growth and subsequent metastasis, which may kill the cancer patient [53]. The final mechanism of the last immunosuppressive category consists of loss or downregulation of surface antigens TAA by tumor cells, which evade the host's immune system by circumventing the cytolytic action of effector T cells (CTLs) due to genetic or epigenetic alterations, which may alter the tumoral protein expression, misleading recognition by the immune system, which promotes uncontrollable tumor growth. Thus, the loss or downregulation of epitopes, such as TAA, and differentiation antigens, such as TRP-1, tyrosinase, MART-1, gp100, and MUC-1, may promote tumoral growth due to escape from the host immune system [54,55]. Furthermore, mutations caused by the tumor in the TAA may circumvent the generation of epitopes, which are recognized immunogenically by cognate CTL regardless of the expression of TAA. These genetic alterations of tumor cells at the coding RNA level may affect posttranslational mechanisms at the protein level, including glycosylation, ubiquitination, and proteolytic enzymes, such as endopeptidases and metalloproteinases (MMPs), which degrade extracellular-matrix (ECM), leading to the downregulation or even total loss of TAA, which mediates tumor escape from the immune system of the host promoting tumor growth.

Thus, there is a continuous struggle between the tumor promoting and the antitumor immune components of the cancer patient where immune promoters of tumor growth and survival include Th17 cell, Cd4+Foxp3+ Treg cells, MDSC, TAM, and their associated chemokines/cytokines, such as TGF- β , IL-23, IL-1 β , TNF, and IL-6, while inhibitors of tumor development and growth consists mainly of CD8+ T, Th1, and CD4+ [56]. The inhibitory signaling pathways to the immune system must be suppressed by cancer immunotherapy [57]. Furthermore, the complexity of cancer involves a crosstalk between tumor microenvironment that interferes with the anticancer activities of the immune system, which in part is caused by the deregulation of the epigenetic machinery that involves methylation-mediated silencing, chromatin remodeling, and microRNA regulons, which may affect immune invasion, tumor-stromal interactions, and tumor angiogenesis [58]. Epigenetic silencing of coding RNA genes, such as retinoblastoma (Rb) gene mediated by histone deacetylase-2(HDAC-2), may regulate immune responses in cancer, which are facilitated by myeloid cells, such as myeloid-derived suppressor cells (MDSCs), polymorphonuclear MDSCs (PMN-MDSCs), and monocytic MDSCs (M-MDSCs), which are the normal counterparts of inflammatory monocytes that differentiate into macrophages, and dendritic cells whose dysfunction in cancer is a severe mechanism of immunosuppression [59,60]. Furthermore, tumor microenvironment (TME) may convert plasmacytoid dendritic cells by complex molecular pathways into tolerogenic immunosuppressive cells [61].

Other tumor microenvironment (TME)-induced immunosuppressive factors, which we must target with cancer immunotherapy not only in solid tumors but also in hematologic malignancies, include tumor intrinsic immunosuppressing ectoenzyme CD37, which is a disulfide-linked homodimer that regulates negatively the proinflammatory effects of extracellular ATP; activates P2X7R, which is a coactivator of the NLRP3 inflammasome-releasing proinflammatory cytokines such as IL-18 and IL-1b; and blocks antitumor T-cell immunity via upregulation of the adenosine receptor (AR) signaling, promoting tumor angiogenesis, growth, and metastasis [62–66].

4. Immunomodulation and immunotherapy

There are many potential therapeutic strategies for circumventing mechanisms of tumor immune evasion, including reversal of the inhibition of adaptive immunity, blocking the T-cell checkpoint pathways such as CTLA4, PD-1, TIM-3, adenosine A2A receptor and LAG-3 checkpoint molecule with agents such as IMP321, BMS-986016, pembrolizumab, nivolumab, pidilizumab, AMP-224, ipilimumab, tremelimumab, etc.

Another therapeutic strategy consists of improving the function of innate immune cells by manipulating the activation of natural killer (NK)-cell inhibitory receptors (KIP) and by stimulating dendritic cells and macrophages with therapeutic agents in clinical development, such as Lirilumab, and Toll-like receptors including TLR 2/4, TLR7, TLR 7/8, and TLR9 agonists, such as Hiltonol, Imiquimod, Resiquimod, CpG7909, and Bacillus Calmette–Guerin.

An additional mechanism consists of switching on adaptive immunity by promoting T-cell costimulatory receptor signaling, using agonist antibodies for the promotion of CD137 signaling with Urelumab, enhancement of CD27 signaling with CDX-1127, activation of CD40 with CP-870,893, and ChiLob 7/4 promotion of GITR signaling with TRX518, enhancement of OX-40 signaling with MEDI 6469, and administration of systemic recombinant IL-7, IL-15, IL-21 with Denenikin, rhIL-7, and rhIL-15 for enhancing immune cell function including T-cell development.

The final therapeutic strategy consists of the activation of the immune system by potentiating immune-cell effector function with IDO inhibition with Indoximab or INCB024360, various vaccine-based therapeutic strategies, inhibition of TGF- β signaling with IMC-TRI, TEW-7197, LY2157299, or GC1008, and systemic IFN- α or IL-2 administration [67].

There are many immunomodulatory effects of targeted therapies, which can circumvent tumor-mediated immunosuppression, improving the effector T-cell function that enhances eradication of targeted tumors. Tumor and immune system effects of approved and experimental targeted agents include Sunitinib, which by inhibiting multiple tumor-associated tyrosine kinases, such as PDGFR and VEGFR, downregulates STAT3 and VEGF signaling pathways, reducing the population and effectiveness of T-reg cells and MDSCs. By blocking tumor-associated tyrosine kinases, such as KIT and ABL, imatinib inhibits IDO, reduces the population and effectiveness of T-reg cells, enhances the population of B-1 B cells and the

concentration of natural antitumor carbohydrate antibodies, and promotes the crosstalk between NK and DC cells. By sensitizing tumor cells to the induction of apoptosis or type I PCD, IAP inhibitors stimulate responses of T cells, NKT cells, and NK cells. GSK3b inhibitors facilitate differentiation toward stem cell memory T-cell population by blocking GSK3b-mediated signaling of tumor cell growth, enhancing TLR4 signaling. By downregulating PI3K-AKT signaling in tumor cells, PI3K-AKT inhibitors enhance tumor susceptibility to perforin and granzyme-mediated lysis involving NK cells and CTLs, downregulating prosurvival signaling and reducing tumor promoting inflammation. By downregulating HSP-90, which enhances unfolded protein-associated stress in tumor cells, HSP-90 inhibitors exert immunostimulatory action by enhancing the expression of NKG2D ligands and by stimulating the CTL recognition of tumor cells. JAK2 inhibitors increase the maturation of DCs, enhance DC-mediated antigen presentation and T-cell priming, and downregulate immunosuppressive STAT3 signaling and expression of IAP and PDL1 of tumor cells by blocking JAK2 signaling in tumor cells. By downregulating BRAF-V600E, vemurafenib upregulates MART1, gp100, and other antigens, while it reduces tumor secretion of immunosuppressive cytokines. By inhibiting 26S subunit of the proteasome, bortezomib sensitizes tumor cells to lysis mediated by CTL and natural killer (NK) cells after the downregulation of the expression of MHC class I molecule, while it boosts antigen-specific T-cell response to vaccination. By inhibiting the mTOR pathway, rapamycin, temsirolimus, and other mTOR inhibitors exert immunostimulatory actions, increasing CD8+T-cell activation and production of IFN- γ , enhancing CD8+ T-cell differentiation into memory T cells, impairing the homeostasis of T-reg cells, and downregulating IDO. Cetuximab as a neutralizing antibody against EGFR inhibits tumoral growth signals and activates the immune system by complement fixation, antibody-dependent cellular cytotoxicity, MHC class I and class II upregulation, and enhancement of DC priming of tumor-specific CTLs. Trastuzumab inhibits tumor growth signaling by the downregulation of HER2, which activates antitumor CTL activity, activates NK cells to secrete IFN- γ , and induces antibody-dependent cell-mediated cytotoxicity (ADCC). Bevacizumab, which is a neutralizing antibody against VEGF, inhibits angiogenesis and subsequent metastasis, while it enhances the maturation of dendritic cells (DCs) and the DC priming of T cells and shifts differentiation of DC toward mature DCs instead of MDSCs [68]. Thus, by interfering with these targeted pathways that drive tumor maintenance and growth, we exert immune therapeutic action by modulating the differentiation, activation, function, and development of the immune cells, which are responsible for inhibiting tumor growth and development, while tumor-induced immunosuppressive mechanisms are circumvented. These immunomodulatory properties that activate the antitumor response include antagonism of tumor-mediated immunosuppressive mechanisms; increase of T-cell activation, differentiation, and effector function; and enhancement of T-cell priming and bolstering of presentation of tumor antigens, indicating a synergistic antitumor action between targeted therapies, which inhibit genomic pathways and anticancer immunomodulatory effects. These synergistic anticancer effects may become even much more effective with the use of combinatorial immunotherapies, which can be used in combination with other conventional anticancer treatment modalities, such as chemotherapy, radiotherapy, and surgery whose inflammatory and immunosuppressive actions may be circumvented with immunonutrition which can improve metabolomics, while

it may circumvent the deadly risk of infection to cancer patients. More analytically, combinatorial immunotherapy may act synergistically by combining two different immunotherapeutic agents, such as inhibitors of immune checkpoints for preventing T-cell energy, and cancer vaccines for producing antitumor T cells. For instance, PD1 inhibitors or CTLA4 vaccines, such as autologous granulocyte macrophage colony-stimulating factor (GM-CSF) secreting tumor vaccine, may exert a significant synergistic antitumor action associated with higher overall survival rates by targeting multiple immunosuppressive pathways. Another combinatorial immune therapeutic approach consists of combining costimulatory receptors, which are overexpressed on activated T cells with agonistic antibodies, leading to enhancement of antitumor T-cell function, which eradicates tumors. Promising combinatorial immunotherapies target synergistically the dual T-cell checkpoints, downregulating CTLA-4, PD-1, PD-L1, and LAG-3 with ipilimumab, tremelimumab, nivolumab, pembrolizumab, MEDI4736, and BMS-986016 against NSCLC, colon Ca, gastric Ca, SCLC, pancreatic Ca, melanoma, RCC, triple (-) breast Ca, and other solid tumors. Combinatorial immunotherapeutic regimens include T-cell inhibitors with costimulatory receptor agonists targeting CTLA-4 and CD40 with administration of tremelimumab and CP-870,893 against metastatic melanoma. Another combinatorial regimen consists of T-cell inhibitors, and function enhancers of innate immune cells targeting CTLA-4, PD-1, and KIR with administration of lirilumab, ipilimumab, and nivolumab against solid tumors. Finally, T-cell inhibitors are combined with other activators of the immune system, such as vaccines and passive immunotherapeutics targeting CTLA-4, IL-21, PD-1, IDO with administration of denenickin, ipilimumab, Nivolumab, INCB024360, indoximod, sipuleucel-T, nivolumab, gp100, NY-ESO-1, TriMix-DC, and adoptive cell transfer against melanoma, prostate Ca, and other solid tumors [67]. Currently, combinatorial therapeutics may combine more than two agents, such as, immunotoxins, Fc-fusion proteins, and bispecific T-cell engagers (BiTEs) [69–72].

Another even more efficient antitumor strategy consists of combining targeted therapies with immunotherapies which exert many antitumor synergies. As we have observed previously antitumor targeted therapies by breaking oncogene addiction, they may optimize the action of immunotherapies by enhancing their sensitivity after circumvention of resistant immunosuppressive mechanisms, leading to elimination of tumorigenic inflammation, enhancing long lived memory T-cell priming, activation, differentiation, function, and effective dendritic cell (DC) maturation, which trigger tumor cell senescence and eradication of tumor cells by induction of apoptosis or type I PCD leading to a bystander killing effect [73]. The derived apoptotic bodies release large quantities of multiple cancer-associated antigenic debris, which activate dendritic cell (DC) functioning as a vaccination in situ, leading to long-lasting remissions by combining the inhibition of oncogenic downstream signaling pathways, enhancing immunosensitivity after elimination of tumor-induced immunosuppressive mechanisms, which may lead to immunomodulatory effects, such as attenuation of the function of specific immunocomponents that block the action of cytotoxic T lymphocytes (CTLs), including myeloid-derived suppressor cells (MDSCs) and FOXP3+ regulatory T (Treg) cells. Other targeted antitumor agents may enhance the priming of tumor-specific CTLs and increase tumor antigen presentation by dendritic cells [74–76].

Thus, this complex interplay of targeted anticancer agents, and immunotherapy may sensitize tumor cells to immune-mediated eradication with long-lasting immunotherapeutic effects, which may inhibit induction of tumor dormancy [77–79].

Thus, we can combine targeted therapies with combinatorial immunotherapies, which consist of conventional immunotherapy, including administration of cytokines and/or chemokines, such as IL-7, IL-15, IL-21, adoptive T-cell transfusion with effector T cells, APC vaccination with dendritic cells (DCs), and tumor-associated antigens with tumor peptides combined with novel tumor immunotherapies, which target tumor-induced immunosuppressive molecules, circumventing tumor immuno-resistance by inhibition of soluble suppressive molecules, such as TGF β , COX2, VEGF, and IL-10; suppressive molecules, such as PD1, and CTLA4 on T cells; and suppressive molecules, such as arginase, B7-H1, B7-H4, and IDO on APCs. They also target immuno-resistant regulatory T cells by inhibition of trafficking with CCL22-specific antibody differentiation and signaling, such as FOXP3 signal, and depletion of T-reg cells with denileukin diftitox, cyclophosphamide, and CD25-specific antibody [80].

These combinatorial immunotherapies with targeted therapies can be used as neoadjuvants and adjuvant treatments with conventional anticancer strategies, such as surgical debulking, radiation therapy, and chemotherapy. For instance, immunotherapies such as indoximod, Denecikocin, CP-870,893, PF-05082566, urelumab, IMP321, pidilizumab, MEDI14763, MPDL3280A, pembrolizumab, tremelimumab, and nivolumab [67], which target CTLA-4, PD-1, PD-L1, LAG-3, CD137, CD40, IL-21, and IDO, have been combined with chemotherapeutic regimens or agents, such as FOLFOX, paclitaxel, cyclophosphamide, carboplatin, docetaxel, gemcitabine, etc., and molecular targeting agents, such as gefitinib, dasatinib, bevacizumab, erlotinib, sunitinib, pazopanid, lenalidomide, vemurafenib, trametinib, rituximab, sorafenib, etc., against liquid tumors, such as CML, NHL, etc., and solid tumors including NSCLC, RCC, multiple myeloma, melanoma, pancreatic Ca, CRC, prostate Ca, breast Ca, etc.

In conventional anticancer treatment, the chemotherapeutic-induced immunosuppression inhibits the anticancer efficiency of cell therapies, which are based on activated lymphocytes for eradication of tumor cells enhancing susceptibility to infections [81]. The majority of conventional chemotherapeutic agents interfere with hematopoiesis and subsequently with the immune system affecting the surveillance of cancer cells promoting tumor development and growth [82].

Generally, cancer surgery causes tremendous alterations in the neuroendocrine, metabolic, and immune systems constituting the stress response, which may lead to infection, and cancer recurrence due to release of catecholamines, cortisol, and cytokines that interfere with the adaptive or specific immunity, which is composed of humoral immunity that consists of B cells, and cellular immunity containing T-cytotoxic cells, T-suppressor cells, and T-helper cells, and the innate or nonspecific immunity. During the postoperative stage, there is balance between pro-inflammatory and anti-inflammatory cytokines. Deficient responses may cause immunosuppression leading to infections. Excessive responses may cause the systemic inflammatory response syndrome (SIRS), which has been associated with the clinical syndrome of sepsis and multiorgan failure (MOF) or multiple organ dysfunction syndrome (MODS) [83].

The postoperative immune response is multifactorial with the release of inflammatory Th1 cytokines, such as IL-6 and TNF- α , and corticosteroids immediately after cancer surgery. Subsequently, even after 2 h from the surgical procedure, there is a reduction of the Th1 cytokines, while the Th2 cytokines, such as TGF- β , and IL-10 rise rapidly increasing the accumulation of immunosuppressive myeloid-derived suppressor cells, and immune-inhibitory cytokines [84]. This shift toward the Th2 immune response deregulates the cellular immunity, enhancing susceptibility of the cancer patient to infection, sepsis, and MOF [85–87]. Furthermore, there is a quantitative reduction of T lymphocytes, which depends on the volume of blood loss during surgery. Also, there is a reduction in the number of white blood cells (WBCs) called leucopenia, which causes immunosuppression that combined with reduced cytokine secretion and suppression of T-lymphocyte responses, and reduced levels of macrophages may cause postoperative sepsis that may lead to morbidity. However, sepsis may be inhibited by postoperative release of anti-inflammatory cytokines, prostaglandins, and nitric oxide, which requires arginine as a substrate for its production by nitric oxide synthase [88]. Since plasma levels of arginine are reduced in septic patients, we need to establish a positive nitrogen balance by supplementation of arginine as an immunonutrition approach. This amino acid regulates blood flow by producing nitric oxide (NO), and it functions as an immunomodulator by enhancing the antitumor cytotoxicity of neutrophils and macrophages [89–92]. Furthermore, the proper antitumor function of T cells requires arginine. The tumor microenvironment contains nitric oxide synthase (NOS) and arginase I, which are upregulated by tumor-induced MDSC, acting as an immunosuppressive mechanism that leads to a deficiency of arginine, which subsequently suppresses the antigen-specific T-cell responses by downregulating the T-cell receptor [93,94]. Within a few hours after cancer surgery, there is an evident reduction of arginine in the circulation of the cancer patient [95,96] because arginine is metabolized by arginase-I, which may be downregulated by omega-3 fatty acids that are metabolized to PGE₃, inhibiting production of immunosuppressive Th2 cytokine, and increasing the production of protectins and resolvins, which promote tissue repair [97]. Immunonutrition in the surgical cancer patient with arginine may improve trauma healing, enhance macrophage function, and lymphocyte immune responses enhancing resistance to infection at the postoperative stage [98]. A functional immune system is required for protecting the surgical cancer patient from the high risk of postoperative infections, which can be achieved by perioperative immunomodulating formulations that can circumvent postoperative immunoparesis and prevent sepsis by activating the immune cell responses, and modulating inflammation.

Other protective perioperative practices include minimally invasive surgical procedures, circumvention of immunosuppressive drugs, and reduction of blood transfusions [99]. Radical surgery combined with old-age neuroendocrine response and administration of analgesics may suppress the activity of the innate immunity and specifically NK cells, which leads to tumor progression since tumor cells circumvent tumor immunosurveillance and subsequent cytotoxicity [100–104]. In addition, operative anesthetics, such as halothane, thiopental, and ketamine, may suppress even further the activity of NK cells promoting metastasis. Thus, immunonutrition may stimulate the immunity, while other factors such as hypothermia, alcohol, and mainly stress may enhance tumor progression [105].

Supplementation with polysaccharides or glutamine may increase natural killer (NK) cell activity [106]. A requirement for a functional anticancer immunity includes a balanced Th1/Th2 ratio because after surgery, a dominant Th2-type immune response, especially in tumors of the gastrointestinal (GI) tract, may suppress tumor surveillance and cellular immunity [107]. Other immunosuppressive and inflammatory factors such as IL-6 and immunosuppressive acidic protein (IAP) may reduce the antitumor activity of cellular immunity leading to tumor progression.

Other immunosuppressive factors include IL-10, TGF- β , and angiogenic VEGF, which is regulated by CD47 signaling that suppresses activity of T cells promoting tumor growth [108]. Thus, after oncological surgery, we must help the patient to maintain homeostasis against the consequences of cancer, tissular attrition, hormonal and metabolic changes, and mainly inflammatory reaction, which induces metastases by a cascade of genomic signaling pathways that may lead to angiogenesis, which is associated to a potent immunosuppression [109,110]. In addition to surgery, other conventional cancer treatments, such as chemotherapy and radiation therapy, may suppress the immune system of the cancer patient by causing a tremendous reduction in the production of all the cells of the bone marrow leading to leucopenia and anemia, which may lead to severe infections. Specifically, if a neutrophil count is below 1000, the risk of infection by bacteria, germs, and fungi is increased, which becomes worse if the count is below 500 where we have neutropenia. This may be treated with administration of colony stimulating factors (CSF) or white blood cell (Leukocyte) growth factors. With bone radiation for metastatic tumors, leucopenia and even neutropenia may be caused by chemotherapy. Furthermore, local radiation therapy can irritate the skin causing small breaks from which germs and bacteria may enter causing infections. Also when lymph nodes are irradiated, infection may occur, which leads to lymphedema. Moreover, there are many tumor-induced immunosuppressive mechanisms, which have been described previously that act synergistically.

5. Immunonutrition

It is very important that more than one third of all cancer deaths are related to nutritional complications, which have been caused by side effects of the major treatments for cancer even the targeted ones. With the administration of nutritional therapy, we can reduce or even inhibit the nutritional complications of cancer, improving nutritional status and healing, maintain normal weight by preventing muscle wasting, and mainly reduce side effects and mortality or morbidity by enhancing the overall effectiveness of anticancer treatments and their combinations while we may preserve and even enhance quality of life. Furthermore, with immunonutrition, we may boost the immune system of cancer patients, especially those who are hospitalized and malnourished. The immune system of cancer patients can be modulated with immunonutritional formulations, which may contain immunostimulant and anti-inflammatory nutrients such as protein, carbohydrate, amino acids, lipids, mineral, trace elements, and vitamins including glutamine, which may enhance immune cell activity, improve nutritional status, and reduce hospitalization time reducing risk of infections. Other

nutraceuticals include arginine, which boosts immune function, prevents infection, and repairs tissue after surgery; omega-3 fatty acids, which have anti-inflammatory properties minimizing the risk for cancer cachexia; ribonucleic acid (RNA), which may stimulate immune cell division and activity; taurine, which reduces inflammation; vitamin C or ascorbic acid, which supports immune function and promotes wound healing; selenium, which supports immune function preventing infection; turmeric, which has anti-inflammatory effects especially at the post-operative stage; vitamins B12, B6, and B1, which may prevent post-operative immunosuppression; zinc, which is important for normal immune system function; and wound healing after surgery [111]. Also, natural products of alternative medicines, such as botanical or herbal plant derivatives, and mind-body practices under an integrative medicine approach may enhance the anticancer effects of conventional anticancer treatments, reducing their systemic toxicity; alleviate clinical symptoms including pain, which are induced by cancer; and prolong survival rates of cancer patients mainly by enhancing tumor immune responses via overexpression of classic MHC molecules, induction of apoptosis in tumor cells via the Fas/FasL pathway, and elimination of oncogenic cancer stem cells by inhibiting tumor immunoresistance [112–115]. Further, alternative medicine therapeutic strategies may reverse the tumor-induced immunosuppressive phenotype regulating the antitumor properties of the immune cells of the cancer patients by enhancing the antitumor abilities of T lymphocytes, regulating the M1/M2 phenotypes of tumor-associated macrophages (TAM), eliminating myeloid-derived suppressor cells (MDSC), enhancing antigen-presenting capacity of dendritic cells (DCs), and regulating the secretion of Th1/Th2 immune factors.

Generally, by using an integrative medicine immunotherapeutic approach where alternative medicine practice which follows a multitargeted and bidirectional regulation may compensate for deficiencies of conventional orthodox western medicine, which is characterized by specificity, we may achieve a synergistic effect concerning circumvention of tumor-induced immunosuppression and enhancement of antitumor immunomodulation followed by minimization or elimination of side effects prolonging the survival rate of advanced stage and metastatic cancer patients promoting their quality of life [116–121].

6. Conclusion

The key is to treat each cancer patient under a precision or personalized evidence-based medicine approach, which must rely on clinomics, including transcriptomics, genomics, immunomics, lipidomics, glycomics, proteomics, metabolomics, nutrigenomics, and mainly epigenomics, whose alterations in their noncoding RNA genes are reversible especially with immunonutrition. The precise immunotherapeutic approach against cancer may act synergistically with conventional anticancer therapies, such as surgery, chemotherapy, and radiotherapy combined with therapies based on molecular targeting, which are tailored for each patient on a pharmacogenomic basis. Also, they can be combined with nanomedicine for specific molecular targeting and circumvention of biological milieu interactions, which may tremendously enhance therapeutic efficacy with simultaneous reduction of systemic toxicity.

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