Immunotherapy and Therapeutic antibodies

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Abstract- Treatment of disorders through immune manipulation of the host has come a long way in the last decades and has broadened its applications from infectious diseases to control of allograft rejection, induction of tolerance for the treatment of autoimmunity and break of tolerance to induce cancer rejection. Immunotherapy, biological response modifier therapy or biotherapy uses the immune system to fight disease like cancer. The potentials of immunotherapy are many. The objective of this review article is to increase awareness of contemporary immunologic therapies and recent advances in immunotherapy.

Keywords- Immunotherapy, Adjuvant, Interleukin, Monoclonal antibody, Interferon, Autoimmunity

Immunotherapy Introduction

Immunotherapy uses the immune system to fight disorders and immune based therapies are to harness the sensitivity, specificity and self-regulation of the immune system to eradicate any and all tumor cells [1]. Biological response modifiers (BRMs) change the route the body’s defenses interact with infected cells and produced in a laboratory and given to patients to enhance immune system. BRMs include nonspecific immunomodulating agents, interferons, interleukins, colony-stimulating factors, monoclonal antibodies, cytokine therapy, and vaccines. Monoclonal antibodies are agents, produced in the laboratories that bind to infected cells. Examples of monoclonal antibody therapy include trastuzumab for breast cancer and rituximab for lymphoma. Chronic disorders including malignant, infectious and autoimmune conditions are difficult to treat and often require the use of multiple agents, alone or in combination. The latter approach is already being attempted in some cancer patients. Herceptin, which targets cell proliferation mediated by HER2 and bevacizumab, which targets tumor angiogenesis mediated by VEGF, are being used in combination in breast cancer patients [2]. Research has been undertaken to provide an explanation on how a relatively limited number of antibodies can protect against a vast and almost infinite number of invading antigens [3]. Proposed potential explanations include the notion that one antibody may be capable of binding more than one antigen through the selection of specific binding sites or pre-existing antibody conformations, and in this manner antibodies with multiple specificities can be achieved. It has been suggested that multispecificity may evolve and play a role in the efficient antibody repertoire for immune protection with one antibody performing more than one task [4]. Autoimmune beneficial from the use of two-in-one antibodies and autoimmune disorders, particularly rheumatoid arthritis and systemic lupus erythematosus, are being treated with single biologic agents directed at specific pathogenic pathways, but one may envision the use of two-in-one antibodies directed at multiple targets in the not too distant future [5]. Cytokine therapy is used with advanced melanoma and with adjuvant therapy and reaches all parts of the body to kill infected cells and prevent tumors from growing. Vaccine therapy involves use of vaccines produced in Escherichia coli, yeast or insect cells. Plant-based vaccines are also advantageous in terms of their scalability, no cold chain required, stability, safety, cost-effectiveness and needle-free administration [6]. Peptide immunotherapy using dominant T-cell epitopes derived from allergens represents another approach to developing safer treatment, because regions involved in allergenicity i.e., responsible for reactivity with IgE, can be completely removed while retaining immunogenicity [7]. Antigen-specific immunotherapy strategies include administration of: proteins/peptides with or without adjuvant; dendritic cells (DCs); transfected with DNA- or RNA-encoding tumor antigens, or loaded with peptides, whole proteins or tumor lysates); recombinant viruses encoding tumor antigens; and autologous or allogeneic tumor cells [8]. Future of immune therapy for cancer holds promise with novel combined approaches that simultaneously target cancer-initiating stem cells, restore APC immune-stimulating activity, expand tumor-reactive T cells and down regulate suppressor pathways to generate effective therapy [9]. Immune therapy for lung cancer has high potential. Identification of the cell type capable of sustaining neoplastic growth and directing immune therapy to cells that possess...
tumor-initiating potential may improve current immune-based therapeutic approaches [10]. Identification of the genetic signatures in cancer stem cells will unravel novel antigens for exploitation in immune therapy protocols with the eventual goal of eliminating residual disease and recurrence [11]. The potentials of immunotherapy are many. The strategy to identify common immunologic themes relevant to human pathology include comparisons of immunologic events necessary for the occurrence of distinct immune-mediated diseases, and we contend that this is most effectively studied following a bottom-up, inductive approach using high-throughput technology [12]. A system immunology approach capable of simultaneously take into account an individual’s genetic background [13], transcriptional patterns associated with distinct diseases [14] and related protein–protein interactions [15], represents the novel formidable challenge that the modern basic or clinical scientists will need to confront to improve the effectiveness of immunotherapy. The understanding of human immune biology and, as a consequence, significant improvements in the effectiveness of immunotherapy will depend on accomplishment of three goals:

• Development of cost-effective strategies for the study of genomic, transcriptional, translational interactions;
• Analysis of the genetic background of the host and its influence on the natural history of disease;
• Analysis of evolving disorders heterogeneity and its influence on its natural history [16].

The limits of monothematic, deductive reasoning applied to human immune biology [17, 18], nonlinear mathematics approaches should be introduced aggressively in the field of immunology since they may better fit the purpose of comprehending the host’s reaction to a pathogenic insult in its globality [19]. The novel strategies combined with traditional deductive reasoning is now called comparative immunology approach. The term refers to parallel analyses of immunological phenomena across species.

**History and Background**

Treatment of disorder through immune manipulation of the host has come a long way in the last decades and has broadened its applications from infectious diseases to control of allograft rejection, induction of tolerance for the treatment of autoimmunity and break of tolerance to induce cancer rejection. Immunity referred to a state of resistance to infectious pathogens. Louis Pasteur’s germ theory provided an explanation for the relevance of an immune status that could recognize proven pathogens. The immune response affected other aspects of one’s organism related to the onset of cancer [20], or the pathologic destruction of own tissues [21]. In 1969, Jonas Salk proposed that delayed hypersensitivity reaction to tuberculin, contact dermatitis, allograft rejection, tumor rejection and autoimmune phenomena represent facets of a similar immune-mediated phenomenon that he termed the delayed allergy reaction [22]. Following Salk’s intuition, immune-mediated tissue-specific destruction can be triggered by distinct mechanisms during allograft or tumor rejection, autoimmunity or pathogen clearance; however, the effector mechanisms converge into an identical final pathway, which termed the immunologic constant of rejection [23].

**Recombinant Simian Glycosylated Interleukin-7**

A new critical function of IL-7 that induces massive and rapid T-cell migration from the blood into various organs, including lymph nodes, parts of the intestine, and the skin has been identified. Homing process was initiated after the induction of chemokine receptor expression by circulating T cells and the production of corresponding chemokines in target organs. It is demonstrated that the IL-7-induced cell cycling is initiated within these organs before T cells migrate back into the bloodstream, indicating that T-cell homing is required for in vivo IL-7 function [24].

**Tolllike Receptor-7 Signaling and Interferon**

Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) constitute distinct families of pattern-recognition receptors that sense nucleic acids derived from viruses and trigger antiviral innate immune responses. TLR3, TLR7, and TLR9 are membrane proteins localized to the endosome that recognize viral double-stranded RNA, single-stranded RNA, and DNA, RLRs, RIG-I, Mda5, LGP2 and are cytoplasmic proteins that recognize viral RNA. Upon recognition of these nucleic acid species, TLRs and RLRs recruit specific intracellular adaptor proteins to initiate signaling pathways culminating in activation of NF-kappaB, MAP kinases and IRFs that control the transcription of genes encoding type I interferon and other inflammatory cytokines, which are important for eliminating viruses [25]. Innate immunity involves contributions of NK (natural killer) cells, DCs (dendritic cells), PRRs (pathogen recognition receptors), PAMPs (pathogen-associated molecular patterns) recognized by PRRs and intracellular signaling pathways. Possible involvement of a newly described group of immune cells, IKDCs (interferon-producing DCs), in innate immunity which show both NK and DC activity is investigated. The mechanisms of innate immunity involves the likely participation of autophagy initiated after endosomal TLR7 (Toll-like receptor 7) activation. Autophagy is able to remove intracellular bacteria or viruses by stimulating type I IFNs (interferons). Especially TLR, activation and inactivation is crucial to avoid an excessive inflammatory response, as occurs...
in autoimmune and infectious diseases [26]. Phagosomal bacteria such as group B streptococcus, but not cytosolic bacteria, potently induces interferon in conventional dendritic cells by a mechanism that requires Toll-like receptor 7, the adaptor MyD88 and the transcription factor IRF1, all of which are localized together with bacterial products in degradative vacuoles bearing lysosomal markers. Thus, this cell type-specific recognition pathway links lysosomal recognition of bacterial RNA with a robust, host-protective interferon response [27]. To balance self-tolerance and immunity against pathogens or tumours, the immune system depends on both activation mechanisms and down-regulatory mechanisms [28]. IFN-beta is used as an effective therapy against relapsing-remitting multiple sclerosis. It is naturally secreted during the innate immune response against viral pathogens. Immunomodulatory mechanisms of IFN-beta targeting innate immune response and their effects on dendritic cell (DC)-mediated regulation of T cell differentiation showed that IFN-beta1a in vitro treatment of human monocyte-derived DCs induced the expression of TLR7 and the members of its downstream signaling pathway, including MyD88, IL-1R-associated kinase 4. NF-kappaB receptor-associated factor 6, while it inhibits the expression of IL-1R, IFN-beta1a-induced changes in MyD88, IL-1R-associated kinase 4, and IL-1R expression depends on TLR7. TLR7 expression was also necessary for the IFN-beta1a-induced inhibition of IL-1beta and IL-23 and the induction of IL-27 secretion by DCs. IFN-beta1a has identified as novel therapeutic mechanism selectively targets the autoimmune response in multiple sclerosis [29]. Plasmacytoid dendritic cells (pDC) are highly specialized immune cells capable of producing large amounts of type I and III IFN in response to viral infection. This response is mediated through TLR7 and TLR9 signaling pathways. Evidences suggest that chronic activation of pDC by endogenous RNA and DNA containing immune complexes maybe an important mechanism of driving autoimmunity and significant efforts to develop bi-functional antagonists of TLR7 and TLR9 are currently underway [30]. Recent experimental and clinical studies have placed new emphasis on the role of the innate immune system in Systemic Lupus Erythematosus. Nucleic acid-containing immune complexes activate the innate response by engaging specific Toll-like receptors (TLRs) and promote the generation of autoantibodies [31]. TRAF6 is involved in the cytosolic RNA- and DNA-induced production of proinflammatory cytokines and type I IFNs. TRAF6 makes crucial contributions to antiviral innate immune responses by sensing not only viral nucleic acids encapsulated in endosomes but also those present in the cytosol. In addition to its role in innate immune responses, TRAF6 is essential for establishing the acquired immune system as a signal transducer of CD40[32], RANK [33, 34], and TCR [35], indicating that TRAF6 is a key molecule for the entire immune system. Therefore, a further understanding of the molecular mechanism associated with TRAF6-mediated signal transduction may help to enable the development of therapies against various immune diseases [36].

Therapeutic Expression of Fusion Inhibitory C Peptides

Tumor necrosis factor alpha (TNF-alpha)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF-alpha family of death receptor ligands and holds great therapeutic potential as a tumor cell-specific cytotoxic agent. TRAIL can selectively kill cancer cells while leaving most normal cells intact [37, 38]. TRAIL kills by binding one of two cell surface receptors, death receptor 4 or death receptor 5. After binding TRAIL, these transmembrane receptors each assemble a death-inducing signaling complex (DISC), the DRs form homotrimers that signal through an adaptor protein, FADD, which recruits the apoptosis-initiating proteases caspase 8, which then self-activates and initiates a signaling cascade leading to apoptosis. Direct correlation between TRAIL sensitivity and constitutive levels of c-myc expression is observed. The knocking down c-myc expression in sensitive cells diminished TRAIL action and expressing c-myc in resistant cells sensitized them to TRAIL [39]. FLICE inhibitory protein (FLIP) is a major regulator of c-myc sensitization to TRAIL. FLIP is structurally related to caspase 8-it contains tandem death effector domains that bind to caspase 8 at the DISC and can block its activation ... [40]. c-myc represses FLIP transcription by binding to the FLIP gene promoter. These suggest that elevated c-myc expression is important in mediating TRAIL action by repressing FLIP transcription and that c-myc may be a potentially useful tumor-specific marker for identifying TRAIL-sensitive tumors. Chronic myelogenous leukemia is typified by constitutive activation of the c-abl kinase as a result of its fusion to the breakpoint cluster region (BCR). The truncated isoform of protein-tyrosine phosphatase receptor-type O (PTPROt) is specifically expressed in hematopoietic cells, it potentially dephosphorylates and inactivate the fusion protein bcr/abl. Ectopic expression of PTPROT in the chronic myelogenous leukemia cell line K562 resulted in hypophosphorylation of bcr/abl and reduced phosphorylation of its downstream targets CrkL and Stat5 confirming, which PTPROT could inactivate the function of bcr/abl. The expression of catalytically active PTPROT in K562 cells caused reduced proliferation, delayed transition from G0/G1 to S...
phase, loss of anchorage independent growth, inhibition of ex vivo tumor growth. Increased their susceptibility to apoptosis, affirming that this tyrosine phosphatase can revert the transformation potential of bcr/abl. PTPRonet expression was suppressed in K562 cells and was relieved upon treatment of the cells with 5-azacytidine, an inhibitor of DNA methyltransferase, with concomitant hypomethylation of the PTPROn CpG island. These data demonstrate that suppression of PTPROn by promoter methylation could contribute to the augmented phosphorylation and constitutive activity of its substrate bcr/abl and provide a potentially significant molecular therapeutic target for bcr/abl-positive leukemia [41].

**Immune Therapies Involving Interleukin-2**

Signaling through IL-2 induces the activation of pathways, which lead to the proliferation survival and cytokine production of effector T cells. Also, through negative feedback mechanisms, internalization of the IL-2 receptor, induction of activation-induced cell death, and the generation of regulatory T cells, IL-2 also promote the suppression of inflammatory responses. In regulatory T cells, IL-2 signaling upregulates the expression of FoxP3 and induction by TGF-beta also requires IL-2. Importantly, IL-2 signaling is key for the development, expansion and maintenance of regulatory T cells. IL-2 not only plays a key role in the induction of effector T cells and regulatory T cells, it also inhibits IL-17 producing T cells. By understanding complex dynamics of IL-2 interactions in the inflammatory response, therapies may be developed or modified for regulating immune related diseases [42]. Conventional treatments such as surgery, radiation therapy and chemotherapy have done little to affect long-term survival of patients with an intracerebral i.e., neoplasm and new methods of treatment are urgently needed. Cytokine gene therapy is a new approach in treatment of malignant brain tumors involving the use of allogeneic cells genetically modified to secrete cytokines. Mice with an i.e., glioma, melanoma or breast carcinoma treated solely by intratumoral injections with allogeneic cells genetically modified to secrete interleukin-2 (IL-2) are found to survive significantly longer than mice in various control groups. Anti-tumor response is mediated predominantly by T-cell subsets (CD8+ and NK/LAK cells). Some of the mice injected intracerebrally with the cytokine-secreting allogeneic cells alone exhibited no neurologic defect and there are no adverse effects on survival. The injection of cytokine-secreting allogeneic cells into the microenvironment of an i.e., tumor is hypothesized to induce an anti-tumor immune response capable of prolonging survival [43]. New forms of therapy to improve the long-term survival of patients with malignant brain tumors are urgently needed. New and novel form of treatment for primary and metastatic brain tumors involves the use of genes involved in growth repression. Immunity can be produced in unique structures on the tumor cells known as antigens. To prepare the vaccine, genes are transferred into a fibroblast cell line that causes the cell to produce cytokines like IL-2, the potent proteins known to stimulate the immune system. These cells are subsequently injected into the tumor bed, resulting in the development of an antitumor immune response. Stimulation of a systemic antitumor immune response was proved by immunocytotoxic studies, histopathological examination, and delayed immune memory responses. Thus, immunogene therapy is a promising new targeted therapy for the treatment of intracerebral malignant tumors [44]. The Preoperative immunotherapy with interleukin-2 may contribute to massive stromal infiltration of immune cells in pancreatic adenocarcinoma. This may prolong the survival even in the presence of negative prognostic factors like age >65 years, tumor diameter >20 mm, R1, tumor grade G3 [45].

**Immune Stimulatory Capacity of Dendritic Cells**

Dendritic cells (DCs) are potent antigen-presenting cells, which are key leukocytes in the initiation of cell-mediated organ graft rejection, antiviral immunity, and antitumor responses. Therapeutic vaccination with dendritic cells (DC) is now recognized as an important investigational therapy. Immunotherapy for leukaemia patients, aiming at the generation of anti-leukaemic T cell responses, could provide a new therapeutic approach to eliminate minimal residual disease (MRD) cells in acute myeloid leukaemia (AML). Dendritic cells can be successfully cultured from leukaemic blasts in 60-70% of patients and show functional potential in vivo. Alternatively, monocyte derived Dendritic cells obtained at time of complete remission loaded with leukaemia-specific antigens can be used as vaccine. Several sources of leukaemia-associated antigen and different methods of loading antigen onto Dendritic cells have been used in an attempt to optimize antitumour responses including apoptotic cells, necrotic cell lysates and tumour-associated peptides. The AML-derived cell line MUTZ-3, an immortalized equivalent of CD34(+) Dendritic cells precursor cells, is under investigation for vaccination purposes.[46] Clinical relevant responses to Dendritic cells based immunotherapy are likely to only occur in non-end-stage patients [47]. Induction of antigen-specific T-cell tolerance in the thymus and its maintenance in the periphery is crucial for the prevention of autoimmunity [48]. The regulatory functions of immature myeloid Dendritic cells, Tr-
cell induction by Dendritic cells 2 represents a nonredundant mechanism for the safeguard of peripheral T-cell tolerance. Dendritic cells 2 can be used as tool to drive potent antigen specific Th-cell differentiation and expansion in vitro and in vivo [49]. Recombinant adenovirus can readily be used for genetic modulation Dendritic cells - induced immune responses in vivo and in vitro. Dendritic cells targeted for induction of specific antigen responses or for modulation of the immune stimulatory capacity may have a potential use in the control of transplantation rejection or viral infections [50]. Dendritic cells are professional antigen-presenting cells, which have an extraordinary capacity to stimulate naïve T cells and initiate primary immune responses. Recent accumulating evidence indicates that several subsets of human Dendritic cells also play a critical role in the induction of peripheral tolerance by anergizing effector CD4(+) and CD8(+) T cells or by inducing the differentiation of naïve T cells into T-regulatory cells, which produce interleukin (IL)-10. These tolerogenic Dendritic cells may be relevant to therapeutic applications for autoimmune and allergic diseases as well as organ transplant rejection [51]. Specific therapy with modulated dendritic cells may restore immunological tolerance, thereby obviating the need for chronic immunosuppression in transplantation or autoimmunity. The tolerizing capacity of dexamethasone (Dex) and 1alpha, 25-dihydroxyvitamin D3 (VD3) modulated Dendritic cells is studied, which demonstrated that both VD3- and Dex-DC possess durable but different differential tolerogenic features, acting via different mechanisms. Both are potentially useful to specifically down-regulate unwanted immune responses and induce immune tolerance. These modulated Dendritic cells appear suitable as adjuvant in antigen-specific clinical vaccination intervention strategies [52].

Interleukin-2 Adjuvant Therapy

Highly active antiretroviral therapy (HAART) induces a substantial control of HIV viral replication [53], but it allows for only a partial immune reconstitution, thus prompting the rationale for the adjuvant use of immunomodulators. Based on its in vitro action as a major T cell growth factor, interleukin (IL)-2 has now been extensively investigated for its potential to correct the HIV-driven immune deficiencies, possibly translating into immunological control over HIV infection. Preliminary results indicate that adjuvant IL-2 induces a significant CD4 cell rescue in patients with no immune recovery following long-term HAART, thus standing as a valid and safe therapeutic option for these patients. Furthermore, in these patients, the IL-2-mediated immune reconstitution is characterized by a rise in both peripheral turnover and de novo T cell synthesis, with reversion of the skewed HIV-driven immunophenotypic pattern, a substantial increase in IL-7 production and in several markers of immune function. These findings indicate IL-2 has a beneficial effect in correcting the severe disruption in T cell homeostasis induced by HIV, through the interaction with T cells and cytokine microenvironment [54].

Monoclonal Antibodies against HCV

Antibodies constitute the most rapidly growing class of human therapeutics and the second largest class of drugs after vaccines [55]. Hepatitis C virus (HCV) infection is the major etiological agent of chronic hepatitis, which leads to liver cirrhosis and hepatocellular carcinomas [56]. A major problem in hepatitis C virus (HCV) immunotherapy or vaccine design is the extreme variability of the virus [57]. Potential for developing efficient and efficacious therapies for hepatitis C virus continues to improve. Insight into the molecular processes involved in attachment, entry, and fusion suggests, which antibodies could potentially inhibit viral replication at any or all of these stages and the attachment and entry stages present the best target for antibodies that can attack the virus. Monoclonal and polyclonal antibodies present an important therapeutic option in this area [58]. The antibodies are shown to be safe, tolerable and could significantly reduce viral load [59]. Monoclonal antibody for hepatitis C virus core antigen consists of microheterogeneous subspecies, which exhibit different antigen binding properties associated with differences in post-translational modification of the heavy chain variable region [60]. Immunoglobulin idiotype is a clonal B-cell marker and an ideal target for immunotherapy [61]. Nonstructural 5A (NS5A) protein of hepatitis C virus (HCV) is a multifunctional protein that leads to pleiotropic responses, in part by regulating cell growth and cellular signaling pathways. Monoclonal antibodies (mAbs) directed against the HCV NSSA protein is produced. N-terminal epitope is mapped to amino acids 60-80 of the NSSA protein and the epitope in the middle region is mapped to amino acids 221-236. These epitopes overlap with binding regions of human vesicle-associated membrane-protein-associated protein (hVAP)-B and TNF-receptor-associated factor 2 (TRAF2) and the action of mAbs for their potential capacity to inhibit viral and cellular interactions is studied. NSSA and hVAP-B interaction is abolished by mAb E5D3, NS5A and TRAF2 interaction is inhibited by mAb C6D4. hVAP-B is necessary for HCV replication and TRAF2 is the major transducer in TNF signaling cascades, these data may provide further insights into the mechanisms underlying HCV replication and viral modulation of host signal
Monoclonal Antibodies against Herpes Virus
In contrast to cell–cell spread within hosts, herpes viruses transmit between hosts as cell-free virions. These are potentially vulnerable to neutralization. Herpes viruses characteristically transmit infection from immune hosts. Glycoprotein B (gB) is the most conserved component of the herpes virus entry machinery and its N terminus (gB-NT) is a common neutralization target. The gB-NT glycans that blocks antibody binding could be targeted for neutralization instead by a lectin, suggesting a means of therapeutic counterattack [65].

CytoGam for prevention of cytomegalovirus infection in kidney transplant patients has recently been granted an expanded indication to include use in lung, liver, pancreas and heart transplant patients [66]. Human cytomegalovirus (HCMV) is a ubiquitous opportunistic virus, which is the most serious pathogenic agent in transplant patients. The available therapeutic armamentarium e.g., HCMV hyperimmune globulins or antivirals, is associated with severe side effects and the emergence of drug-resistant strains; therefore, neutralizing human mAb may be a decisive alternative in the prevention of primary and re-activated HCMV infections in these patients. Recombinant human monoclonal IgG1 suitable as a prophylactic or therapeutic tool in clinical applications has been generated from immune B cells [67]. Characterization and recombinant expression of a glycoprotein-B-specific antibody is done. The genes encoding the Fab part of the antibody are cloned and expressed in Escherichia coli. Recombinant Fab fragments specifically binding the extracellular domain of glycoprotein B could easily be isolated from the periplasmic space. Recombinant antibodies provide the opportunity to modify effector functions and to add tags to diagnostic antibodies for more efficient detection of CMV-infected cells [68].

Monoclonal Antibodies against Human Immunodeficiency Virus (HIV)
Most existing viral vaccines generate antibodies, which either block initial infection or help eradicate the virus before it can cause disease. Target of HIV-specific nAbs, the viral envelope glycoprotein (Env), is highly variable in amino acid sequence and glycosylation pattern. Conserved elements of HIV-1 Env seem to be poorly immunogenic, and previous attempts to generate broadly reactive NAbS by vaccination have proven ineffective. Also, recent studies show that antibodies in the sera of some HIV-1-infected individuals can neutralize diverse HIV-1 isolates [69]. HIV-1 has evolved a number of strategies to evade humoral immunity, including protecting highly conserved and important structures from the access of antibodies generated by the immune system. Human dAb (size approximately 15 kDa), m36, targets a highly protected structure on the HIV-1 envelope glycoprotein (Env), gp120, and exhibits exceptionally potent neutralizing activity against HIV-1 primary isolates, with potency on average higher than those of the broadly cross-reactive neutralizing human monoclonal antibody, scFv m9, and the inhibitory peptide, C34. Engineered human antibody fragments, dAbs, could be more potent because of their small size (about 10-fold smaller than that of an IgG3), which allows targeting of highly conserved structures on the HIV-1 envelope glycoprotein that are not accessible by full-size antibodies and relatively efficient penetration into the densely packed lymphoid environment in which HIV-1 mostly replicates and spreads [70]. Recently developed novel approaches are based on sequential (SAP) and competitive (CAP) antigen panning methodologies and the use of antibodies with increased exposure of conserved epitopes, for enhanced identification of bcnAbs to gp120-gp41. The antibodies identified by using these approaches (X5, m6, m9) bind better to gp120-CD4 complexes than to gp120 alone (CD4i antibodies); they exhibit exceptional neutralizing activity and breadth of neutralization as scFVs and on average lower potency as Fabs and IgGs [71]. To identify human monoclonal antibodies with high activity against HIV and broad-spectrum activity, a technique termed sequential antigen panning is developed. This methodology could be used to isolated recombinant antibodies against any antigen that shares epitopes with other antigens [72]. More than 20 million people have died since the discovery of human immunodeficiency virus (HIV). Interest in anti-HIV nAbs has been revived by the impressive protection achieved in primates given passive...
immunization with neutralizing monoclonal antibodies (nmAbs) isolated from HIV clade B-infected individuals. The nmAbs used in these studies target conserved, functionally important epitopes in HIV gp120 and gp41. The existence of these broadly reactive nmAbs suggests that it may be possible to design immunogens capable of inducing similar nAb responses by active vaccination. Unraveling the three-dimensional structures involved in the nmAb-HIV Env epitope interactions may facilitate the future development of a potent AIDS vaccine [73]. The third variable loop (V3 loop) of the HIV-1 pathogen’s gp120 surface envelope glycoprotein can be a highly sensitive neutralization target. Sequence motifs for the V3 loop epitopes recognized by the human monoclonal antibodies (mAbs) 447-52D and 2219 is derived. Many assays confirmed that the epitopes corresponding to these motifs, when expressed in the SF162 Env backbone, were sensitively and specifically neutralized by the respective mAbs. More importantly, these calculations demonstrate that globally relevant, structurally conserved epitopes are present in the sequence variable V3 loop [74]. A model for intrapartum and milk-borne HIV transmission by orally challenging neonatal macaques with chimeric simian-human immunodeficiency viruses (SHIVs) has been established. Safety and efficacy of passive immunization with human neutralizing monoclonal antibodies (nmAbs), which had been isolated from HIV clade B-infected individuals, which target conserved, functionally important epitopes is tested. The nmAbs studied are F105 or IgG1b12, b12 for short (directed against the CD4 binding site), 2G12 (anti-gp120), 2F5 and 4E10 (both anti-gp41). Passive immunization with currently available anti-HIV clade B nmAbs could play a role in preventing transmission of non-clade B isolates through breastfeeding [75]. Molecular interaction between the peptide/MHC class I complexes (pMHCs) and T cell receptor (TCR) is fundamental to the effector function of cytotoxic T lymphocytes (CTLs). Monoclonal antibody against pMHC with TCR-like specificity is a possible research tool for the antigen presentation. A successful generation of monoclonal antibodies against an HIV-1 CTL epitope loaded on an MHC class I molecule is provided by the work of Nunoya et al. To isolate monoclonal antibodies against an immunodominant HIV-1-derived CTL epitope in the nef gene, phage clones from a human scFv phage display library is used [76].

Conclusion

Immunotherapies hope to attract outstanding and novel concepts, whether generated though discovery or hypothesis-driven approaches that may enhance the understanding of human biology and with this the effectiveness of immunotherapy. The goal of immunotherapy is the development of novel clinical vaccine protocols and strategies to induce therapeutic T-cell responses as a successful therapeutic approach. Although significant advances have been made in the field of immunotherapy for different types of cancer, important challenges remaining are when to immunize, what antigens are best targeted, what vaccine-type combined with what adjuvant has the best trade-off between immunogenicity and clinical applicability and how to overcome immune escape by tumor cells. Various types of immune-based therapies are under development which might be used as a monotherapy or in combination with other antiviral drugs for the treatment of chronic HCV infection. Vaccination, as an antidepressant therapy, may invoke several molecular and cellular pathways which are known to be regulated by antidepressant drugs. Specific therapy with modulated dendritic cells may restore immunological tolerance, thereby obviating the need for chronic immunosuppression in transplantation or autoimmunity. Cytokine gene therapy is a new approach in treatment of malignant brain tumors. By understanding complex dynamics of IL-2 interactions in the inflammatory response, therapies may be developed or modified for regulating immune related diseases. A system immunology approach capable of simultaneously take into account an individual’s genetic background, transcriptional patterns associated with distinct diseases and related protein–protein interactions, represents the novel formidable challenge that the modern basic or clinical scientists will need to confront to improve the effectiveness of immunotherapy. Optimal way to integrate novel immune targeted combinations will be the major focus of future studies and will require a coordinated and cooperative multidisciplinary effort by the international scientific community.

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