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CYTOTOXIC T CELLS AND CANCER THERAPY

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ABSTRACT

The cytotoxic T lymphocyte (CTL, T_c) is a type of T lymphocyte/ white blood cell involved in the host's cell-mediated immune response against cancerous cells, abnormal cells and cells infected with viruses. Signals from infected cells or cancer cells lead to the release of cytotoxins: perforin, granzymes, and granulysin by the T_c cells. The activation of CTLs is mediated by the interaction of various co-stimulatory molecules as well as immune cells. Pre-eminent role of CTLs in combating cancer can be effectively applied for the active and passive immunotherapeutic approaches. Various recombinant cytokines viz., interleukins (IL)-2, 4, 7, 10, 12, 15; tumor necrosis factor (TNF) have been found to augment the production of CTL. CTLs can also be stimulated in antigen specific manner through tumor antigens which are the molecular derivatives over expressed in tumorcells due to differentiation, point mutations or viral origin. Designing and development of vaccines based on such immunogenic candidates can be executed and in majority of cases such antigens are targets for CTLs. Identification as chemotherapy and CTL-mediated killing, and validation of these CTL-specific antigens require

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monitoring that can be done by various new techniques including enzyme-linked immunospot (ELISPOT); tetramer analysis, proteomic analysis and detection of cytokine intracellularly. Role of CTLs in various types of cancer including lung cancer; virus-induced lymphoproliferative disease as well as cervical cancer; gastrointestinal cancer have been discussed vividly. In the present review, role and applications of CTLs in cancer therapy has been described with a special attention on focusing the genetic approaches for adoptive CTL therapy as well

1 Introduction

In the later part of the 19th century one of the lengthiest goal in developing immunotherapy against cancer has been achieved. In this quest developments in the recent years have rejuvenated the optimistic sense. Few of the malignant cancers can now be treated by employing monoclonal antibodies (MAbs) which are highly specific and can provide accurate diagnosis. Apart from conventional anti-cancer therapeutics available, some of the upcoming therapeutic regimens include cytokines (Dhama et al., 2013a), tumor homing peptides (Khandia et al., 2016a), heat shock proteins (Khandia et al., 2016b), zootoxins (Mohanty et al., 2016), bacterial toxins (Khandia et al., 2017a), cell penetrating peptides (Khandia et al., 2017b), nanotechnology-based drugs (Iqbal et al., 2016; Ahmad et al., 2017), biomarkers guided therapy (Dadar et al., 2016); immunotherapy and molecular approaches (Dhama et al., 2014; Acharya et al., 2015; Dhama et al., 2015); apoptosis (Kumar et al., 2015); herbs and plant metabolites like Guduchi, Noni, green tea etc. (Dhama et al., 2013b; Saminathan et al., 2013; Dhama et al., 2016), panchgavya elements (Dhama et al., 2013c) and others. These are crucial advances of course but it is suggestive on the basis of much more evidences that harnessing of the cellular immune system may prove more efficacious to the endeavour (Maher & Davies, 2004; Abbas et al., 2007; Zou & Restifo, 2010). Cytotoxic T lymphocyte (CTL) is the other name of cytotoxic T cell; also known as T-killer cell; cytolytic T cell; CD8+ T-cells or killer T cell; T_C. Such type of T lymphocyte/white blood cell helps to destroy cancer cells particularly the ones that are virus-infected. A specific antigen which is produced by cancer cells or virus-affected cells is recognized by most cytotoxic T cells which express T-cell receptors (TCRs). The class I Major Histocompatibility Complex (MHC) bind antigens inside a cell and bring them to the cell surface where their recognition is done by T cells. For the binding of TCR to the complex of the class I MHC molecule, a glycoprotein known as cluster of differentiation (CD) 8 must accompany the former so that it can bind to the constant portion of the class I MHC molecule. Thus, such T cells are known as CD8+ T cells. The binding of T_C and the target cell is helped by the affinity between CD8 and the MHC molecule during the antigen-specific activation. Once activated, there is recognition of the CD8+ T cells as T_C cells. Cytotoxic role is therefore

performed by them within the immune system. Even though the CTLs are tiny (measures about a tenth of the human hair width) they certainly form crucial line of defence against infections as well as tumours (Wilke et al., 2011; Hivroz et al., 2012; Dhama et al., 2013a; Hoyer et al., 2014).

It is a fact that CTLs mediate defence against abnormal or infected cells but cannot recognize free/naive antigens in circulation. Cellular defence of CTLs is induced by the recognition of endogenously processed antigens expressed on the surface of infected/cancerous cells along with MHC I molecules. CTL antigen binding is therefore always restricted to the MHC determinants correctly. The CTLs thereafter proliferate as well as differentiate. There is promotion of this event by a variety of cytokines viz., interleukin (IL)-1; IL-2; as well as IL-12. There is unique alteration morphologically in association with the activation of CTL (antigen-specific). There is therefore increase in cell size; they become polarized, highly forming lysosomal granules uniquely that contain a pattern of lytic proteins specifically. A sequence of predetermined steps is followed by the target cell lysis via CTL. This include: binding of killer-target cell; delivery of lethal hit; target cell lysis; and killer cell recycling. Following the recognition of appropriate antigen, CTL firmly binds to the target cell surface on the basis of presence of Mg²⁺ (but not Ca²⁺). Subsequently two different mechanisms mediate target cell lysis; exocytosis of lytic proteins; and/ or binding of receptor-ligand (of Fas molecules) (Groscurth & Filgueira, 1998; Freiberg et al., 2002; Taniguchi et al., 2003; Jahng et al., 2004; Gabrilovich & Nagaraj, 2009). This review focuses on how cytotoxic T lymphocytes (CTLs) may be used as target for immunotherapy against cancer; especially lung cancer and certain virus-induced cancers.

2 Effector functions of T_C cells

On exposure to infected/ dysfunctional somatic cells there is release of cytotoxins viz., perforin, granzymes, and granulysin by the T_C cells. Granzymes enter the cytoplasm of the target cell via the action of perforin. The serine protease functions to trigger the caspase cascade, which is a chain of serine proteases eventually leading to apoptosis. Otherwise it is referred to as programmed cell death. Interaction between the T_C and the infected cells is a second mode of induction of apoptosis. The T_C upon activation

expresses FAS ligand (surface protein)/ FasL (Apo1L) (CD95L) (binding to *Fas* (Apo1) (CD95) molecules and target cell expressing them). However the interaction between Fas-Fas ligand is crucial as far as the disposal of unwanted T lymphocytes or lytic activity of certain T_H cells are concerned. The death-induced signalling complex (DISC) is recruited when Fas is engaged with FasL. Pro caspases 8 as well as 10 are recruited due to translocation of the Fas-associated death domain (FADD) with the DISC. This is followed by activation of effector caspases 3, 6

and 7. This causes cleavage of death substrates like lamin A; lamin B1; lamin B2; poly ADP ribose polymerase (PARP); and DNA-activated protein kinase (DNAPK). This leads to the final result which is nothing but the cellular apoptosis on the basis of expression of Fas (Matteo et al., 2005; Subramanian & Ramalingam, 2005; Matteo et al., 2006; Gabrilovich & Nagaraj, 2009; Milstein et al., 2011; Lui-Roberts et al., 2012). The mechanism of tumor cell killing by CTLs has been illustrated in Figure 1.

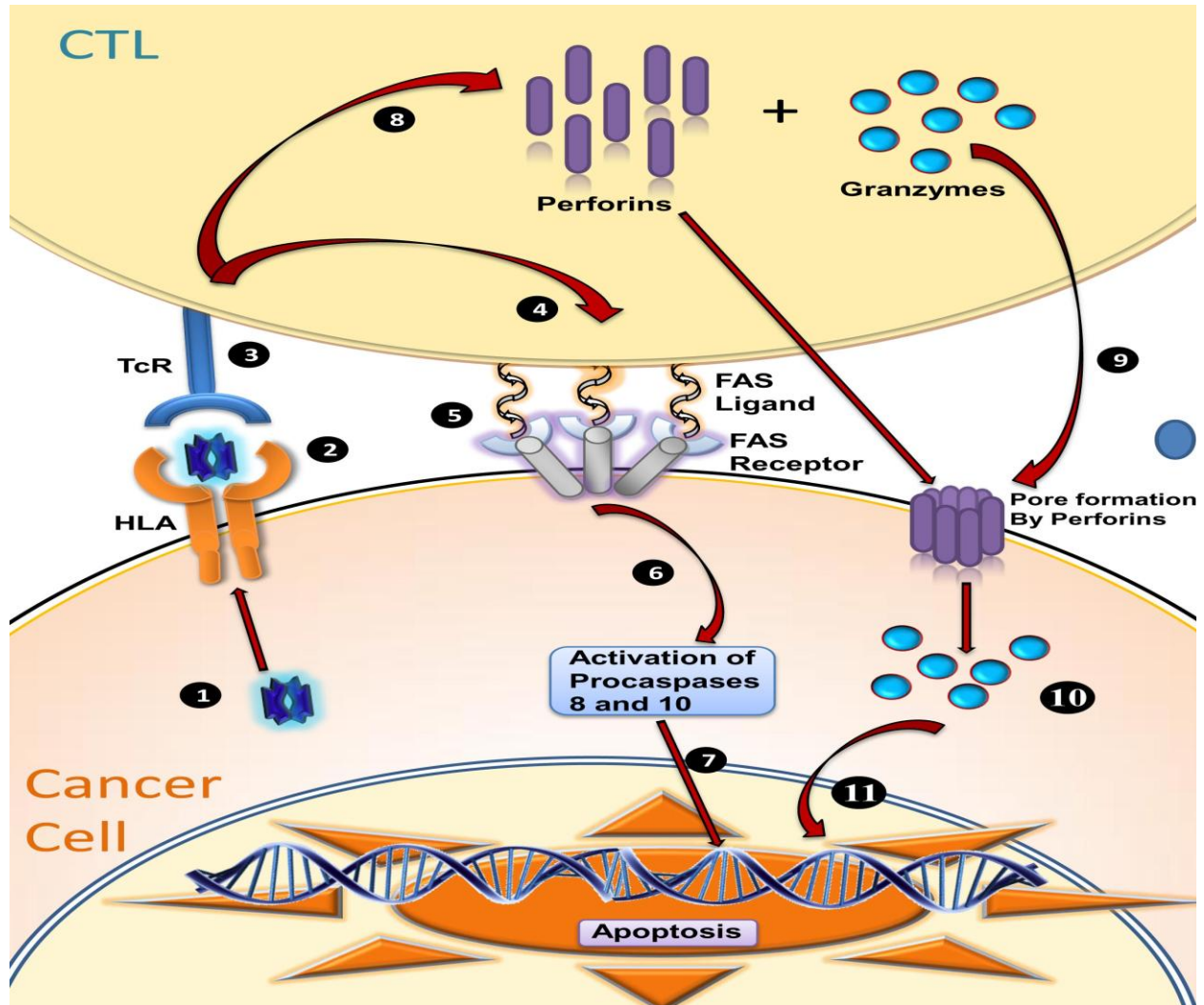


Figure 1 CTL mediated cancer cell killing (1) Tumor specific proteins are expressed in cancer cells (2) Tumor peptides are processed and presented over the surface of cell by HLA molecules (3) HLA presented peptide is recognized and bound by CTL (4) Binding initiates cascade of reactions for expressing FAS ligand (FASL) to (5) Engage FAS receptors present on the tumor cell (6) Leading to initiation of activation of procaspase 8 and 10 (7) and result in subsequent apoptosis (8) CTL produces perforin and granzymes (9) Perforin are polymerized to form pore into cancer cells and (10) Granzymes enters the cancer cells through the pore formed by perforins and (11) cleaves functional proteins and DNA to cause apoptosis.

potent immunological functions CTLs can be employed in case of malignancies of various origin due to expression of MHC class I molecules in wide spread fashion. These are over the time recirculated for seeking out antigen; a single peptide-MHC class I complex can elicit effector CTL mediated cytolysis pathway with high avidity for target recognition (Sykulev et al., 1996; Hanlon et al., 2002; Qin et al., 2003).

Effector CTLs are regulated by depending on the naive CD8⁺ T cells (antigen-driven in nature) differentiation, and when dendritic cells (DC) get in contact with antigen. This results in migration to the regional lymph nodes. Here with naive T lymphocytes there is interaction of the DCs. The result is recirculation through secondary lymphoid tissue. The DCs must be in activated state for achieving optimum CTL priming and is achieved when there is presentation of processed antigen to MHC class II-restricted CD4⁺ helper T cells. Then there is subsequent upregulation of CD40 ligand thereby causing engagement of DC-associated CD40 (Lanzavecchia, 1998; Hayakawa et al., 2001; Fujii et al., 2004; Kumar et al., 2015).

CTLs interact with cognate target cells with a dual activation threshold, resulting in the formation of two distinct synapses; the lytic synapse at CTL-target cell contact site for cytotoxicity and the stimulatory synapse for activating cytokine production (Faroudi et al., 2003). The effector responses from CTLs over each target cell are executed effectively by rapid lethal hit and subsequent cycling of action on other target cells (Isaaz et al., 1995). Some cellular studies point out the CTLs exhibiting simultaneous killing of multiple target cells also, but yet to be validated *in vivo* (Friedl et al., 2005). This blending of serial^l and multiple target cell destruction facilitates effective immune surveillance and thus CTLs embodies the diversity and complexity in its effector mechanisms in the course of immune responses in eliminating abnormal cell/infected cells in pathological tissues (Wiedemann et al., 2006). CTLs are provided with strong antigenic stimuli through sustained synapses with target cells, thereby polarizing the lytic granules towards different cells and along with spatiotemporal uncoupling of immunological synapses enables the multiple killing (Callan et al., 1998; Alegre et al., 2001; Hayakawa et al., 2001; Vinay et al., 2004; Wiedemann et al. 2006).

CD4 T cells render crucial assistance in promoting cytotoxicity and survival of effector CD8 T cells especially in chronic infections and in establishing memory cells following primary response (Rajasagi et al., 2009; Phares et al., 2012). They also facilitate the entry of primed CTLs from regional lymphoid tissues into sites of infection/ abnormality (Smith et al., 2004; Nakanishi et al., 2009) and these assistance in terms of CD4 T cells are unrelated to Th effector phenotypes i.e., both Th1 and Th2 cells can mediate these functions (Ekkens et al., 2007).

CD8⁺ T memory cells are clinically important as they function directly *in situ* as cancer killer cells. The current knowledge however is suggestive of the fact that CD8⁺ T cells seem to be more simplified functionally in comparison to the CD4⁺ T cells. The reason behind is that for a stronger consensus clinically there is only one outcome due to the presence of a simple killer at the site of tumour. A high concentration of suppressor CD8⁺ T cells has also been noticed in patients suffering from cancers. Detection of such cells at the site of tumour can thereby reveal another layer of complexity (Andersen et al., 2009; McNally et al., 2011; Azimi et al., 2012; Kumar et al., 2015).

3 Immune tolerance and cancer

For counter action of the attention of CTL as well as other effector arms of the immune system various immune evasion strategies are adopted by cancer cells, many of which rely upon the capability of cancer cells to harness systems maintaining immune tolerance to self. Immune tolerance could happen by removing the auto reactive lymphocytes via an immunotherapeutic strategy. For therapeutic manipulation, in contrast non-deletional tolerance mechanisms work better. For instance, it has been implicated through more evidences that immune tolerance is maintained by various regulatory T cell sub sets that may include classical Treg cells (CD4⁺ CD25⁺) and other associated T cells like Tr1 cells (produces IL-10); Th3 cells (produces transforming growth factor (TGF)- β); and CD8⁺ regulatory T-cell subsets. These immune-suppressive cells can induce tolerance towards both self and derived malignancies (Jonuleit et al., 2001; Stinchcombe & Griffiths, 2001; Nelson, 2004; Pasero et al., 2016; D'Errico et al., 2017). However, by deleting or suppressing these cellular populations, immunotherapy of malignant diseases could be strengthened (Maher & Davies, 2004). It is exciting to notice that checkpoint blockades are utilized nowadays for blocking signals that are negative thereby maintaining the response to tumours. Molecules on the surface of T cells like cytotoxic T lymphocyte antigen 4 (CTLA-4) play significant role in regulation of check point (Grosso & Jure-Kunkel, 2013; Makkouk & Weiner, 2015).

4 Role of Natural killer T (NKT) cells in induction and activation of CTLs

It has been reported in various studies that type I NKT cells' activation is found in intimate association with the cancer cell elimination. These are lymphocytes which are unique by the expression of a single invariant antigen receptor that recognizes glycolipids associated with CD1d molecule. Since they can mediate immunopotentiating activity towards CTLs as well as NK cells, leading to the extermination of tumours without relapse, NKT cells can be very-well employed in anti-tumorcellular therapy (Brigl & Brenner, 2004; Fujii et al., 2006; Lippitz, 2013; Taniguchi et al., 2015). Induction of NKT cell-targeted anti-

tumortherapy can be mediated by either IL-12 or –GalCer but difference in the stimulatory substances can lead to various patterns of cytokines production. When IL-12 is administered it can lead to production of high amount of Th-1 cytokine (or interferon's) in type I NKT cells dependent manner/ fashion; whereas both Th-1 (Interferon's) and Th2 (IL-4) cytokines are secreted on activation by –GalCer (Takahashi et al., 2000; Metelista et al., 2001; Prlic et al., 2003; Ambrosino et al., 2007; Kumar et al., 2015; Shanker et al., 2017). In the induction as well as activation of CTLs various cytokines; co-stimulatory molecules as well as immune cells play crucial role. Various recombinant cytokines viz., IL-2, 4, 7, 10, 12, 15; tumornecrosis factor (TNF) have been found to augment the production of CTL. The degree of enhancement depends on the specific antigen; population of cells that are responding; and several environments. Particularly IL-2 has got the potential to cause induction of particular cytotoxicity (Ludewig et al., 1999; Uldrich et al., 2005; Ito & Seishima, 2010; Dhama et al., 2013a).

5 Vaccination strategies targeting CTL to tumorantigens

For developing vaccine against cancer, one traditional approach involves the use of whole tumorcells (inactivated). There has been more recent extension of this approach along with the development of vaccines based on tumorcells which have been engineered for expression of immunomodulatory cytokines as well as co-stimulatory ligands; like that follows genetic modification or fusion with DCs (Freigang et al., 2005).

Non-viral malignancies have also been reported to express tumorantigens. On the basis of defined molecular targets there have been developments in vaccines and in majority of cases such antigens are targets for CTLs. They are derived from molecules which are over expressed in tumorcells in comparison to their normal counterparts (Van der Bruggen et al., 2002). One of the key obstacles to the breaking of the immune tolerance to cancer is recognizing close relationship between tumorantigens and 'self'; a wide variety of vaccines (antigen-specific) are under development on the basis of peptides; protein; mRNA or DNA that are expressed from plasmid or viral vectors (Whelan et al., 2003; D'Errico et al., 2017). A panel of adjuvants promoting DC activation to enhance immunity has been reported (Cerundolo et al., 2004). Several tumorvaccines show expanded CTL responses for useful applications (Coulie & van der Bruggen, 2003; Morris et al., 2003).

Various clinical studies on the therapeutic vaccination have been performed recently on small scale basis in recent years. The safety of the approach has been confirmed by these trials in general. CTL stimulation and antibody responses have been well documented against vaccine components (Knutson et al., 2001). This is suggestive of the fact that tumours expressing defined

antigens can be immunotherapeutically targeted (Finn, 2003; Morris et al., 2003).

Characterization of tumour-associated antigens has paved way for newer avenues in cancer therapy, recognized by cellular and humoral immune effectors. As targets for CTLs *in vitro* as well as *in vivo* there have been description of various types of cancer-associated antigens viz., cancer-testis (CT) antigen; melanocyte differentiation antigen and viral antigens; apart from those arise from point mutations or over expression of critical genes in malignant tissues. Several antigen-derived peptides based on these tumors associated antigens have been revealed to induce specific CTL responses through various *in vivo* clinical studies. Immunological and clinical parameters are available for assessing peptide-specific reactions (like induction of delayed type of hypersensitivity; autoimmune as well as tumour- regression responses). Tumour-associated antigens also cause elicitation of CTL-responses that lead to regression of tumorfollowing injection intradermally. There is tumorregression brought about by CTLs induced through peptide immunization.

Active immunotherapy with tumour-associated antigens is a promising approach to cancer immunotherapy. As a result, patients have residual disease to the minimal level. There has been human leukocytic antigen (HLA)-A2 restricted CTL reactivity in melanoma patient with antibody having higher titer against cancer-testis antigen (Jafer et al., 1999; Johnson et al., 2002; Terabe et al., 2000; Terabe et al., 2005). Tumorvaccination in case of advanced stages of tumorproves to be relatively ineffective; but in patients with sub-advanced malignancies suitable vaccines can be of much effectiveness (with minimal residual disease). Tumor vaccination can be employed in association with other therapeutic modalities as proven to be effective in case of promyelocytic leukaemia (Padua et al., 2003; Le et al., 2010). Also, multivalent vaccines against tumors may be a viable approach as they prime CTLs to target multiple epitopes (Graff-Dubois et al., 2002). CTL responses (antigen-specific) require monitoring that can be done by various new techniques including enzyme-linked immunospot (ELISPOT); tetramer analysis and detection of cytokine intracellularly (Kurzrock, 2000; Clay et al., 2001). For antigen delivery materials-based strategies involving use of nanoparticles (polymeric); virus-like particles; liposomes; peptidomimetics etc have been adopted for enhancing immunity based on CD8⁺ T cells (Chesson et al., 2017).

6 Adoptive CTL therapy

There is a wide range of suitable CTLs that target several tumours at present. The first clinical tests of adoptive transfer of CTLs have been permitted by improvement in CTL cell culture technology. This approach produces an immune response which is productive and vividly studied in patients suffering from

melanoma (Perica et al., 2015). Patients suffering from refractory; metastatic melanoma can be treated in this way using CTLs that are infused following ex-vivo potentiation. These are (MART-1) CD8⁺ T cells which recognise melanoma antigen efficiently destroy normal melanocytes as well as tumours that are MART-1 negative. This demonstrates a tumorvariant selection with the loss of expression of MART-1. In an independent trial, such results are confirmed in such a manner that there is CTL engraftments. This is subsequently measured by a high rise in the level of T cells that are circulating and are able to bind tetramers that are fully loaded with MART-1 peptides. But the anti-tumorresponse rate is very low in patients even though the level of engraftment in patients is high. Even though CTL transfer facilitates a potent means to combat tumorgrowth, some adverse conditions still pertain and most prevalent among them is the emergence of antigenic variants. This is more reflected in human cases of tumours than with mouse syngeneic tumormodels (Norell et al., 2006).

Clinical trials based on CTL transfer in melanoma patients revealed its vaccine-like action resulting in epitope spreading. This suggesting the possibility of addressing antigenic variation and immune evasion of tumorcells through the enhancement of immune response by infusing CTLs possessing multiple antigenic specificity or by increasing efficiency to spread epitope (Marincola et al., 2000; Yee et al., 2000; Yee et al., 2002; Mackensen et al., 2006; Norell et al., 2006; June, 2007; Dhama et al., 2013a; Maude et al., 2014; Rahal et al., 2014). Improvement in adoptive cell therapy towards refractory melanoma has been developed with autologous tumorinfiltrating lymphocytes (TIL) from patients and applied in combination with recombinant interleukin-2 and non-myeloablative lympho-depleting chemotherapy (NMA). NMA conditioning of patients which is to be done before infusing the potentiated T cells, diminishes the endogenous regulatory T cells and other interfering cells, thereby enabling the survival of transferred cells (Rosenberg et al., 2011; Besser et al., 2013). It follows the demonstration of the fact that IL-2 can help to achieve responses in a small number of patients. The response rate is moderately improved upon infusion of TIL. Over period of time TIL are found to be enriched for CTLs that are MHC class-I restricted. They are specific for melanoma that are known and include: MART-1 as well as gp 100. Impressive expansion of TIL (IL-2 driven) *in vivo* has been observed that causes significant increase in the clinical response rate (Rosenberg et al., 1994; Dudley et al., 2002).

7 Genetic approaches to adoptive CTL therapy

Advances in gene manipulation and cell culturing techniques deliver robust means for redirecting the specificity of T cells so that CTLs with high receptor specificity and potent cytotoxicity against tumorcells can be generated for immunotherapy (Norell et

al., 2006). Some prominent genetically modified anti-cancer T cells are those with chimeric antigen receptors (CARs) or neoantigen-specific T-cell receptors that are extensively used in adoptive immunotherapy as promising candidates in combating tumorcell immune evasion (Morris & Stauss, 2016; Ye et al., 2017). Development of various investigative avenues for the expansion and increase in the specificity of adoptively transferred T cells is still under process. One among them is the application of antigen-presenting cells (artificial) permitting CTL (tumour-specific) expansion *in vitro* and has come up with promising results. In order to achieve this, NIH3T3 fibroblasts have been genetically engineered, permitting the expression of peptide epitopes in the way similar to that of endogenous peptide i.e., in association with an MHC class I molecule and a β 2 microglobulin along with series of co-stimulatory ligands. IL-15 as growth promoter has been recognized by various researchers in order to boost *in vitro* expansion of CTLs.

Chimeric antigen receptors are genetically engineered receptors on the surface of CTLs wherein an antibody derived single chain fragment (scFv) is coupled with intracellular signalling element via a hinge region (Maude et al., 2014). On the surface of T cells usually CARs are expressed as homodimer (coded by a single gene) enabling recognition of tumour-associated antigen in MHC-dependent manner (Kirkwood et al., 2008). There have been constructions of various fusion receptors of such kind. These have been constructed with molecular specificity expressed by malignancies that are solid as well as haematological in nature (Latouche & Sadelain, 2000; Brentjens et al., 2003; Maher & Davies, 2004; Kirkwood et al., 2008).

Since T-cell co-stimulation is not provided by most tumours, the subsequent area of interest has become the CAR development that can provide such type of accessory signals. Initial developments focused on the construction of fusion receptors of scFv (or CD28) and recently designed CAR with the fusion of signalling domains of CD3 ζ and CD28. Repeated activation of such cells is facilitated by co-culturing with tumorcells (expressing antigens *in vitro*) and tumortargets die rapidly with each cycle of stimulation. This is followed by proliferation of CAR-grafted CTLs that are IL-2 driven. For the CAR-grafted CTLs to survive over a sustained period of time an approach is specific gene transfer into T cells responsive to Epstein-Barr Virus (EBV). They are known to persist for a prolonged period of time *in vivo* and thereby facilitating a sustained control of a tumorburden *in vivo* and provide momentum to CAR technology (Haynes et al., 2002; Maher et al., 2002; Rossig et al., 2002; Finney et al., 2004). The clinical responses against blood cancers by the use of CAR T cells are quiet noteworthy (Kershaw et al., 2014). Work is in progress to develop CARs delivering two or more co-stimulatory molecules. An alternate system to redirect the specificity of both

CD4⁺ and CD8⁺ T cells is developed by associating a defined TCR (tumor-associated) that is specific for a new MHC-peptide complex and has been tested with success in several *in vitro* studies (Maher, 2012; Sharpe & Mount, 2015). Permission has been granted to a greater repertoire of attractive protein antigens compared to CAR and evidences suggest that in comparison to ectopic TCR the immunogenicity of CAR derived from rodent hybridoma based scFv is found to be greater. Such advantages are however balanced by certain disadvantage like: there is requirement of co-expression of two gene products in a regulated fashion i, e. α and β chains of TCR (as the TCR is a heterodimer). In principle TCR sub units (that are endogenous in nature) may form heterodimer with such exogenous receptor subunits. This can lead to generation of complexes with potential of auto-reaction. It is possible to overcome this potential difficulty by including sequences permitting only dimerisation of the ectopic TCR sub units (Gilboa, 1999; Eberl et al., 2000; Fujii et al., 2003; Hermans et al., 2003).

The microenvironment inside the tumor growth is critical with regard to the outcome of immunotherapy as it is often poorly conducive to the function of CTLs. There can be overproduction of immunosuppressive cytokines viz., TGF- β (in case of several malignancies), which can however be circumvented by genetic approaches. Suitable immunopotentiating agents like LIGHT (belongs to the tumor necrosis factor superfamily) can be genetically employed for manipulating the microenvironment alternatively. This is the reason why there are reports of recruitment of naive CTL dramatically. They get primed there eliciting anti-tumor immunity which is impressive in nature (Gorelik & Flavell, 2001; Yu et al., 2004).

8 Role of cytotoxic T- cells in various types of cancers

8.1 Lung cancer

There is increased efficacy of treatment of both small cell lung cancer or non-small cell lung cancer (NSCLC) with the activation of the immune system. Clinical efficacy of immunomodulatory antibodies directed against cytotoxic T cell-associated antigen 4 (CTLA-4/CD152) and programmed cell death ligand 1 (PDL1/CD274) is evident too. CTLs are the main immune cells having anti-tumor activities. The pre-requisite for the immune system to attack the cancer cells is the availability of these tumor-directed CTLs both in numbers and functionality. Lung cancer suppressive capability is known to be possessed by two types of immune cells (playing a pivotal role in patients) viz., regulatory T- cells and suppressor cells (myeloid-derived) (Matsui et al., 1999; Ikeda et al., 2004; Aerts & Hegmans, 2013). At the same time the greater rate of survival in case of NSCLC is in close association with effector T cell (CD3⁺CD8⁺) infiltration (Aerts et al., 2014).

8.2 Lymphoproliferative diseases caused by Epstein-Barr virus (EBV)

Much interest to utilize cytotoxic T cells as adoptive immunotherapy for viral as well as malignant diseases has been stimulated by an increase in the understanding of the mechanisms by which there is recognition of T lymphocytes that recognize virus as well as tumour-specific antigens. A mild as well as self-limiting illness caused by EBV in immunocompetent hosts. This is followed by a latency (life long period) wherein cytotoxic T cells (that are EBV-specific) control the viral activity in the B cells. There is involvement of EBVs in case of malignancies viz., Hodgkin's disease as well as nasopharyngeal carcinoma (NPC). There is development of lymphoproliferation that remains unchecked in hosts with impairment of immunity to T-cell thereby leading to immunoblastic lymphoma (Curiel, 2007). In patients receiving bone marrow from family members who are mismatched or unrelated donors the frequency of such complications are highest. This happens if there is lack of T cells in the marrow to prevent graft-versus-host disease. In the unselected lymphocyte population EBV-specific T cells are contained from the blood of the donor peripherally. They can be utilized to control lymphoproliferative disease (caused by EBV). Complications may arise due to the presence of alloreactive T cells in the lymphocyte infusion. This in turn restricts the utilization of such therapy. Generation of EBV-specific cytotoxic T cell lines have been done from donor lymphocytes for the purpose of overcoming this obstacle. They can be used against lymphoma induced by EBV prophylactically. The infused CTLs are marked genetically to reliably monitor the cells for both their persistence and localization within the body. It has been found that such CTLs that are gene-modified can persist for an extensive period of time *in vivo* for retaining anti-EBV activity (Beatty et al., 1997; Rooney et al., 1998; Sakaguchi, 2000; Shankaran et al., 2001; Curiel, 2007).

9 Post transplant lymphoproliferative disease (PTLD) and nasopharyngeal carcinoma (NPC)

PTLD is characterized by the proliferation of B lymphocytes in an immuno-compromised patient. After undergoing organ transplantation, patients used to medicate with immunosuppressive drugs to prevent an impending organ rejection. This results in an uncontrolled proliferation of lymphoid cells (Dharnidharka et al., 2016). Epstein-Barr virus (EBV), a member of the herpes virus family, has been found to be involved in PTLD as a consequence of life long persistence of EBV following its primary infection (Dharnidharka & Araya, 2009). Since Cytotoxic T lymphocytes (CTLs) can control PTLD, the adoptive immunotherapy using autologous EBV-immortalized lymphoblastoid cell lines (LCLs) has been employed for more than ten years, thereby stimulating CTL expansion in an EBV-

specific manner (Abbas et al., 2007). The success of PTLT treatment has encouraged in conducting various studies to know the CTLs (activated EBV-specific) causing regression of advanced NPC. It has been thereby found that there is certainly clinical benefit of such treatment especially in patients with locoregional disease (Sherritt et al., 2003; Straathof et al., 2005). It is interesting to note that there has been demonstration of the fact that peptide vaccination may prove efficacious as has been understood by conduction of clinical trials in human. Based on this, patients with NPC are being treated using EBV-specific CTLs for assessing the potential use of adoptive transfer of CTLs (peptide activated). It has been found that in this particular disease expression of EBV gene is limited to latent membrane protein (LMP) Following adoptive transfer the infused cells containing LMP2 specific CTLs are well tolerated. Basically, the infused CTLs are not apparently found to be effective in curtailing the growth of primary tumormass in patients. Moreover, when the plasma samples of the patients have been collected a peak in the EBV DNA have been observed which is the proof of the fact that the NPC cells have undergone lysis by the action of these infused CTLs. It is also interesting to note that there is possibility that the CTLs have better access to lungs when infused (Abbas et al., 2007; Kenter et al., 2008; Kenter et al., 2009; Lutzky et al., 2014).

9.1 Human papilloma virus (HPV)-induced cervical cancer

It has been found that IL-10 combinedly with IL-2 can cause consistent increase in cytotoxicity. Cytotoxic activity of transfused HPV CD8⁺ T cells (E7-specific) was proven to be potentially effective against cervical cancer. In other words, it can be said that the expansion and potentiation of CTL activity (tumour-specific) is augmented by a combination of IL-10 and IL-2 for clinical use in the therapy of cancer (Santin et al., 2000). Also, cytotoxic CD8⁺ T cells (HPV-specific) when generated *in vitro* by E-7 pulsed autologous DC, were efficient in destroying naturally autologous tumorcells (HPV-infected) when applied in patients suffering from invasive cervical cancer. Dominance in expression of intracellular type I cytokine by the human leukocytic antigen (HLA) class I- restricted CTLs has been noted i, e. there is higher levels of expression of IFN- γ ; IL-2; and TNF- α ; and low level of expression of IL-4 (Pittet et al., 2000; Santin et al., 2000; McHugh et al., 2001).

8.2 Gastrointestinal (GI) cancer

The advanced stage of GI cancer is a virulent disease with a poor prognosis inspite of multidisciplinary treatment. For clarification of the effects of CTLs (tumorspecific) therapy clinically as a multidisciplinary treatment for patients having cancer at advanced state studies has been conducted. It is crucial to note that there is distant metastasis in case of patients having advanced stage of GI cancer and is derived from gastric cancer; colon cancer; as well as

bilio-pancreatic cancer. After providing adoptive immunotherapy based on CTLs it has been observed that such patients develop no severe toxicity. However, there is development of fever as well as myelosuppression. Clarification has been done and it has been found that as multidisciplinary treatment CTL therapy is valuable clinically particularly in terms of standards of life. As a mode of development of new cancer prevention strategy cancer vaccine which is carcino embryogenic antigen (CEA) specific have just been started (Tsunoda et al., 1999; El-Omar et al., 2003; Zhang & An, 2007).

10 Chemotherapy and CTL-mediated killing

A serious challenge is faced by immunotherapy against cancer due to low efficacy clinically. As per recent clinical study reports the clinical response rate is higher in case of several types of cancer when cancer vaccine and chemotherapy are used, Various anti cancer vaccines and chemotherapeutic drugs have been tested in mice along with approaches to transfer adoptive T cells. The tumorcells become more susceptible to the effect of cytotoxic CTL due to chemotherapy (Zou, 2006; Dhama et al., 2013a). This is achieved in the body by making tumorcells increasingly permeable to granzyme B (perforin-independent) using drugs viz., paclitaxel (TAX); cisplatin (CIS); and doxorubicin (DOX) etc. which can then sensitize tumorcell to CTLs. These drugs act via up regulation of mannose-6-phosphate receptor expression on the surface of tumorcell. Apoptosis can be introduced in neighbouring tumorcells by using chemotherapy and CTLs (raised against specific antigen) combinedly without those antigens getting expressed. It is therefore suggestive of the fact that CTLs in small numbers can mediate anti-tumoreffect potentially together with chemotherapy (Veugelers et al., 2006; Zou, 2006; Zitvogel et al., 2008; Ramakrishnan et al., 2008; Ramakrishnan et al., 2010). Docetaxel (a taxane) has been found to increase the susceptibility of tumours of human origin to CTL mediated killing (Hodge et al., 2013). Studies have shown that the CTL percentage increases in patients with breast cancer when treated by following epirubicin regimen (5-fluorouracil; epirubicin; and cyclophosphamide) (Bracci et al., 2014).

Conclusion and future perspectives

The researchers have described cytotoxic T cells as serial killer due to their antigen-specific cytolytic action towards cancer through CTL clones with unique TCR and they certainly play definitive role to keep good health. Features such as the ability to mount defence against malignancies of diverse origin due to the ubiquitous expression of MHC class I molecules, immunity against systemic diseases through the continuous recirculation throughout the body, highly sensitive target recognition even with very little peptide-MHC complex, indirect anti-tumor action especially by non-lytic effector mechanisms through interferon

gamma etc. render them as promising candidates of anti-tumor immunity. In our body, the CTLs are billions in numbers recognizing the cancerous cells through markers on the cell surface. It has been demonstrated by scientists that in the cell packaging parts of the body the lethal hit must be focused by the CTLs on the target exception to which may lead to collateral damage to the cells of the neighbouring regions that are healthy. There is sealing of the fate of the cancer cell once there is injection of cytotoxins into the cancer cells resulting in its death. Researches have been conducted much vividly to explore the role of CTLs in cancer immunotherapy and for development of T cell based vaccines. Various trials based on cellular immunotherapy have come up with clinically proven potential of CTLs in adoptive immunotherapy against cancer cells. But advances are still warranted in this field for the expansion of CTL based therapy in terms of quickly targeting tumorantigens (relevant) *ex vivo*, potency in preventing the recurrence of tumor once treated, and cost-effectiveness of the therapy thereby making it more potential and popular in countering different cancerous conditions.

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