Introduction

Genetic or epigenetic alterations in somatic cells lead to abnormal growth of tissues , this uncontrolled growth is termed as tumor which could even spread to other parts parts of the body in some cases known as malignant tumor while destined to its own position only is termed as benign tumor[1]. Many therapies are used for treatment depending upon the stage of cancer. Chemotherapy remains one of the major therapeutic option for different malignancies despite having surgical and radiation treatments. Approaches like immunotherapy, phototherapy , gene therapy have been developed to avoid resistance to drugs[2].
Carcinoma, sarcoma, leukemia are one of the three main groups of cancer. Carcinoma are referred to as malignancy of epithelial cells , Sarcoma arise from solid tumors of connective tissue while leukemia arise from blood cells and immune cells. Interaction with genetic factors and 3 types of external agents are responsible for cancer- physical carcinogen (ionizing radiation), chemical carcinogen, biological carcinogens (bacteria, viruses or parasites and pathogens). Various imaging tests like Ct scan , X-ray, ultrasound etc. are performed for screening along with lab tests[1].
Loss of MHC I expression and of other proteins involved in processing of antigenic peptides like TAP1 etc. are responsible for the metastatic growth of tumors[3]. CD4+T cells play role in anti tumor activity.

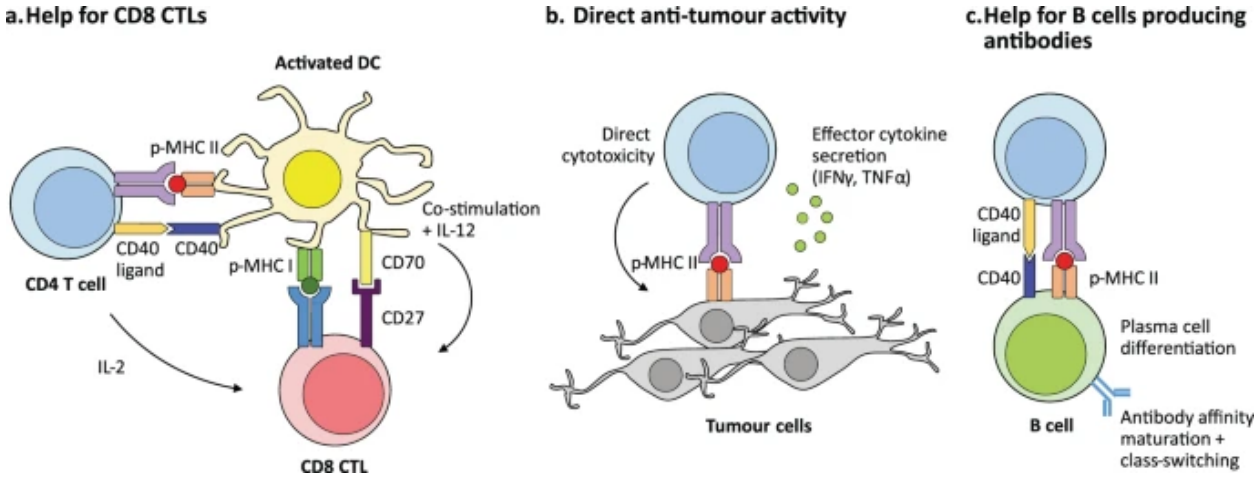

fig1.Mechanism of CD4+T cells playing role in tumor immunity[4]

CD4+T regulatory cells comprise of major subset of CD4+ T cells, distinct from conventional CD4+ effector T cells. Observation that CD4+ T cells synergise with CD8+ T cells in immune response extends to CAR T cell therapy[4].

Therapy with Objective Function

1) **CYTOKINE THERAPY**- Ability of cytokines to prevent death of activated T cells may play an important role . IFN type I and II, GM CSF, IL-2, IL-7, IL-12, IL-15, IL-21 have been evaluated in clinical trials for immunotherapy in cancer(typeII interferon , GM-CSF, IL-2, IL-21 has T cells as target)[5].

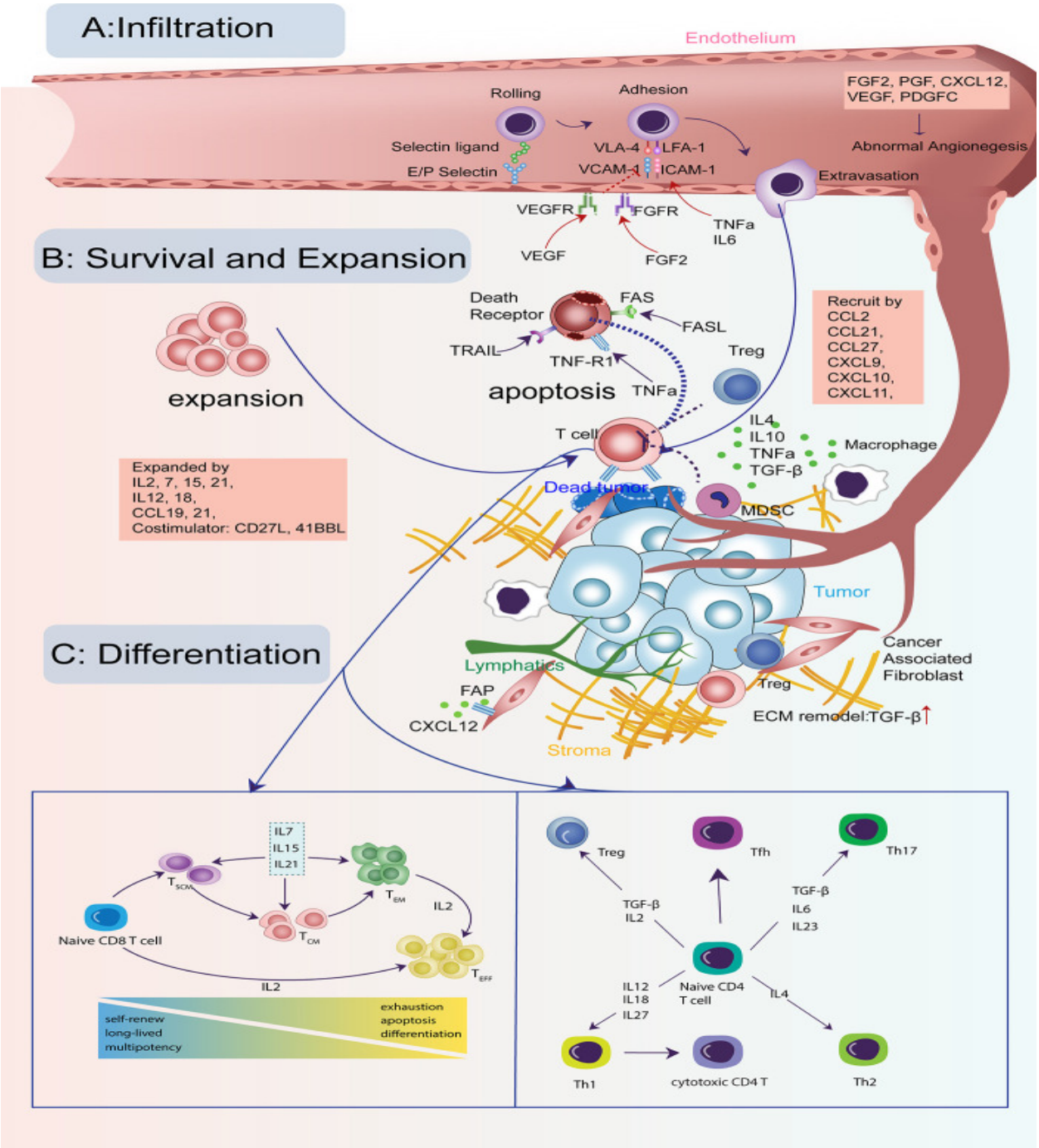

fig2.Cytokine signals in life span of T cells in tumor[5]

The effectiveness of cytokine therapy is to increase the proportion of effector cells,cycling cells and decrease the proportion of progenitor, terminal exhausted cells.
The goal is thus to identify the gene (out of all 15,077 possible genes that passed quality control) that when knocked out would lead to a larger proportion of effector cells,cycling cells and a smaller proportion of progenitor, terminal exhausted cells.
More specifically, we define the desired ideal cell state proportion vector to be Q=(0,1,0,1,0) where as in Challenge 1 the cell states are ordered as ('progenitor', 'effector', 'terminal exhausted', 'cycling', 'other').

Let Pi=(ai,bi,ci,di,ei) be the predicted cell state proportion vector for knocking out gene i. We define the **objective function** to be

bi/qo -ai/po - ci/ro + di/so

where each denominator corresponds to the proportion of cells in the respective state as computed among the unperturbed cells, so as to weigh each state similarly. Here larger score indicates a better perturbation

ai=predicted proportion of progenitor cells for knockout gene i (Pi[0])
bi=predicted proportion of effector cells for knockout gene i (Pi[1])
ci=predicted proportion of terminal exhausted cells for knockout gene i (Pi[2])
di=predicted proportion of cycling cells for knockout gene i (Pi[3])

po=predicted proportion of progenitor cells for unperturbed cells (Po[0])
qo=predicted proportion of effector cells for unperturbed cells (Po[1])
ro=predicted proportion of terminal exhausted cells for unperturbed cells (Po[2])
so=predicted proportion of cycling cells for unperturbed cells (Po[3])

2) **MONOCLONAL ANTIBODIES THERAPY**- Bispecific monoclonal antibodies could be used that would bind to tumor cells on one part and other part could bind to proteins like CD3 on immune cells like T cells thus bringing cancer cells and immune cells together causing immune system to attack tumor. Monoclonal antibodies (mAbs) could be directed against inhibitory receptors such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1)[6].

Generic Name (Trade Name)	Species of Origin	Isotype	Toxic Payload	Target	Indication	Refs

Unconjugated Antibodies

Trastuzumab (Herceptin)	Humanized	IgG1	-	HER2/*neu*	Breast Cancer
Rituximab (Rituxan)	Murine-human Chimeric	IgG1	-	CD20	Lymphoma
Cetuximab (Erbitux)	Murine-human Chimeric	IgG1	-	EGF Receptor	Colorectal Cancer
Bevacizumab (Avastin)	Murine-human Chimeric	IgG1	-	Vascular Endothelial Growth Factor	Colorectal, Lung, Breast Cancers
Alemtuzumab (Campath-1H)	Humanized	IgG1	-	CD52	Chronic Lymphocytic Leukemia

Immunoconjugates

Ibritumomab tiuxetan (Zevalin) plus	Murine	IgG1	Yttrium	CD20	Lymphoma
Rituximab	Human	IgG1			
131ITositumomab plus	Murine	IgG2a	131Iodine	CD20	Lymphoma
Tositumomab (Bexxar)					
Gemtuzumab (Myelotarg)	Human	IgG4	Calicheamicin	CD33	Acute myelogenous

Table1- therapeutic monoclonal antibodies approved for use in oncology[7]

The effectiveness of monoclonal antibodies therapy is to increase the proportion of effector cells and decrease the proportion of progenitor, terminal exhausted, and cycling cells.
The goal is thus to identify the gene (out of all 15,077 possible genes that passed quality control) that when knocked out would lead to a larger proportion of effector cells and a smaller proportion of progenitor, terminal exhausted, and cycling cells.
More specifically, we define the desired ideal cell state proportion vector to be Q=(0,1,0,0,0) where as in Challenge 1 the cell states are ordered as ('progenitor', 'effector', 'terminal exhausted', 'cycling', 'other').

Let Pi=(ai,bi,ci,di,ei) be the predicted cell state proportion vector for knocking out gene i. We define the **objective function** to be

bi/qo -ai/po - ci/ro - di/so

where each denominator corresponds to the proportion of cells in the respective state as computed among the unperturbed cells, so as to weigh each state similarly. Here larger score indicates a better perturbation

ai=predicted proportion of progenitor cells for knockout gene i (Pi[0])
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po=predicted proportion of progenitor cells for unperturbed cells (Po[0])
qo=predicted proportion of effector cells for unperturbed cells (Po[1])
ro=predicted proportion of terminal exhausted cells for unperturbed cells (Po[2])
so=predicted proportion of cycling cells for unperturbed cells (Po[3])

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