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HLA-E (Human Leukocyte Antigen-E): Promising Biological agent for Cancer Mitigation

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ABSTRACT -

Traditional surgical or chemoradiotherapeutic methods typically cannot eradicate metastatic cancer cells, and disease recurrence is very common after treatment. On the other hand, stem cell-based therapies are becoming more and more promising for the treatment of cancer. By homing in on and concentrating on both primary and metastatic tumour foci, stem cells can serve as innovative delivery systems. In preclinical animal models, stem cells modified to stably express different cytotoxic drugs reduce tumour sizes and lengthen longevity. They have also been used as virus and nanoparticle carriers to lessen the negative effects of treatment and improve the effectiveness of initial therapies. Additionally, stem cells can be used in immunotherapy, cancer stem cell-targeted therapy, and applications for anticancer drug screening. However, although treating human malignancies with stem cells.

Keywords

Cancer, stem cell, connexins, chemotherapy

INTRODUCTION

Due to population increase and ageing, cancer is a primary cause of death in both industrialised and developing nations, and it is a growing global medical burden. Chemotherapy, fractionated radiation, and surgical resection are the main cancer treatments. However, the effectiveness of many therapeutic choices is constrained by treatment-related adverse effects, off-target effects, and drug resistance. Additionally, conventional medicines typically are unable to eradicate cancer cells that have spread to other parts of the body, making recurrence highly likely. As a result, scientists are attempting to create novel, efficient medicines with minimal to no damage in normal cells. Stem cells are the building blocks from which all other cells with specific roles are derived in the body. The appropriate circumstances in the body or a lab allow stem cells to proliferate to create more cells termed.

Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells .Cancer is a genetic disease—that is, it is caused by changes to genes that control the way our cells function, especially how they grow and divide.

Genetic changes that cause cancer can happen because:

- Due to errors that occur as cells divide.
- Due to damage to DNA caused by harmful substances in the environment, such as the chemicals in tobacco smoke and ultraviolet rays from sun.
- Due to inheritance from our parents.

STEM CELL

Stem cells are defined by their ability to:

1) Self-renew indefinitely

2) Form single cell-derived clonal cell populations, and

3) Differentiate into various cell types

Stem cells can be divided into main three categories: embryonic, somatic/Adult, fetal stem cell, umbilical cord stem cell.

1. Embryonic stem cell

Embryonic stem cells (ESCs) are found in the inner cell mass of the human blastocyst, an early stage of the developing embryo lasting from the 4^{th} to 7^{th} day after fertilization. In normal embryonic development, they disappear after the 7^{th} day, and begin to form the three embryonic tissue layers. ESCs extracted from the inner cell mass during the blastocyst stage, however, can be cultured in the laboratory and under the right conditions will proliferate indefinitely. ESCs growing in this undifferentiated state retain the potential to differentiate into cells of all three embryonic tissue layers

2. Adult/Somatic Stem Cells Introduction

Adult stem cells are undifferentiated cells that reside among differentiated cells in a tissue or organ. They have the ability to renew themselves and differentiate into specialized cell types. Not like embryonic stem cells which can become all cell types, adult stem cells are limited to differentiating into distinct cell types of their tissue of origin, and they are therefore multipotent or unipotent stem cells. The primary roles of adult stem cells are to maintain and repair the tissue in which they reside. Adult stem cells are rare and generally small in number, but they can be found in a number of various tissues of the adult organism. The most studied are stem cell populations present in bone marrow (hematopoietic and MSCs), intestine, and skin, but there are distinct populations residing in many other organs, such as in the central nervous system, liver, mammary gland or dental tissues.

3. Fetal Stem Cells

Fetal blood and bone marrow including other fetal tissues such as the liver and kidney can be the source of the fetal stem cells. Fetal blood contains hematopoietic stem cells (HSC) and these proliferate more rapidly than those present in adult bone marrow or cord blood. Non-hematopoietic mesenchymal stem cells (MSC) are also present in the first-trimester fetal blood that supports haemopoiesis and differentiate along multiple lineages. Fetal stem cells have been known for better intrinsic engraftment, multipotentiality and lower immunogenicity as compared to adult stem cells.

4. Umbilical Cord Stem Cells

The type of stem cells which are harvested from the umbilical cord after childbirth are cord blood stem cells. These kinds of cells can be preserved in cell banks for future use. Numerous diseases such as blood cancers and genetic blood disorders have found hopes for treatment with the umbilical cord blood stem cells.

The Potential Applications of Stem Cell Therapy in Cancer

Various strategies have been developed for cancer treatment using stem cell therapy, includingHSC transplantation, MSC infusion for post-cancer treatment, stem cells for therapeutic carriers,generation of immune effector cells, and vaccine production

HSC Transplantation

HSC transplantation has been primarily used as a standard procedure for the treatment of multi-ple myeloma, leukemia, and lymphomas after rounds of high-dose radiotherapy or chemotherapy(clinicaltrials.gov). In addition, this procedure is now widely investigated in clinical trials, incombination with chemotherapy or immunotherapy, to treat other kinds of cancer, such as braintumors (NCT00528437), neuroblastoma, sarcomas (NCT01807468), and breast cancer. However, the occurrence of graft-versus-host-disease (GVHD) when using allo-geneic sources of HSCs remains a challenge, which is often treated with immunosuppressive drugswith less effectiveness and serious side effects

Stem Cell Source for Production of Immune Cells

Chimeric antigen receptor (CAR) T cells and natural killer (NK) cells have been successfully applied for anticancer immunotherapy. These clinical-grade immune cells are often harvested from the own patient, activated, genetically transduced with CAR constructs, expanded, and then rein-fused to the patient. However, controlling the quantity and quality of those cells for immunotherapy remains challenging, especially in patients who experienced heavy chemotherapy or in whom with higher ages. In addition, in vivo anti-tumor activity of these CAR immune cells is of-ten limited due to their rapid differentiation into short-lived effector cells. Therefore, there are requirements for the generation of CAR cells from other sources, which enables the expansion of this immunotherapy to a larger number of patients. Human pluripotent stem cells, including iPSCs and ESCs, could offer unlimited sources for this purpose.

Stem cell transplantation to recover immune system

Stem cell transplantation (SCT) is the procedure that can recover the marrow function for patients who have severe marrow injuries or damaged immune. Stem cell for transplantation can come from bone marrow, peripheral blood, or umbilical cord blood. There are many terms for stem cell transplantation, including bone marrow transplantation, cord blood transplantation, or hematopoietic cell transplantation. These different names are used for the same procedure. There are two common types of transplantation including autologous and allogeneic stem cell transplantation.

With autologous stem cell transplantation, patients use their stem cells. This type of transplantation is used for cancer patients who exposure with a high dose of chemotherapy or radiation therapy. Such high doses of treatment are used to eliminate cancer cells, but can severely damage bone marrow and immune system. Therefore, in order to preserve stem cells, those are collected from bone marrow or blood before treatment, then frozen. Later on, thawed stem cells are re-infused into a patient in order to restore function of the immune system. Because stem cells come from patient's own, the immune system recovered by stem cell does not attack patient's tissue. However, those could be contaminated with circulating cancer cells and may increase the risk of rellapse of disease. Furthermore, the recovered immune system could be stronger, but does not have the ability to eliminate the remaining cancer cells since those cancer cells may tolerate to patient's immune system

Stem cells as vectors carrying therapeutic reagents to tumors

In gene therapy for cancer treatment, stem cells are used as vehicles to carry drugs or therapeutic vector viruses to tumors. Stem cells possess two crucial advantages that determine their potential application for gene therapy: tumor tropism and immune-privilege.

Stem cells have intrinsic characteristics to migrate toward the injury sites to support repairing. Cancer is a form of lesion inside the body. Thus, mesenchymal stem cells are postulated to have the ability to migrate towards tumors. In fact, tumors secrete cytokines such as TGF-β, IL-8, EGF, HGF, FGF, and PDGF. These secreted cytokines stimulate MSCs to upregulate chemokine production and expression of chemokine receptors and then making MSCs more able to migrate to the tumor site.

Many studies have used MSCs and neural stem cells (NSCs) to carry suicide enzymes to the tumor site. This approach is expected to avoid systemic toxic effects and leave normal cells intact. Prodrug-activating systems that are commonly used are cytosine deaminase/5-fluorocytosin herpes simplex virus thymidine kinase/ganciclovir. Once engineered stem cells reach the tumor, the suicide enzymes activate 5-fluorocytosine or ganciclovir to a drug that attacks crucial metabolic pathways in the cells, leading to cell death .Active drugs are able to attack neighboring cancer cells via the gap junction, intracellular communication, and connexins; this process is known as bystander effect. MSCs- based gene therapy has been used to treat several diseases in animal models including glioblastoma, prostate cancer melanoma, gastrointestinal cancer and other malignancies. Along with MSCs, neural stem cells (NSCs) carrying suicide enzyme have shown to reduce tumor volume and to increase survival in mouse model of malignant disease including medulloblastoma melanoma brain metastases , glioblastoma , breast cancer brain metastases , prostate cancer , and breast cancer

Stem Cells as Therapeutic Carriers

Genetic modification enhances the therapeutic potential for stem cells in oncology by facilitating precise secretion of bioactive mediators. Typically derived from bone marrow, endogenous mesenchymal stem cells (MSCs) migrate towards sites of damaged tissue. MSC tropism is propagated by a cascade of signaling mechanisms and chemokines which trigger the recruitment of MSCs towards sites of damaged tissue.MSCs are able to mobilize effectively as they express numerous chemokine receptors including: CCR1, CCR2, CCR4, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, and CX3CR1.Additionally, MSCs possess the ability to produce a diverse array of cell adhesion molecules which facilitate the engraftment to specific target tissue.Upon transplantation, MSCs will migrate away from the initial injection site into a tumor microenvironment (TME) before engrafting to various target cells. Therefore, the transduction of MSCs and other multipotent stem cells could potentially facilitate the decisive delivery of a therapeutic payload within a tumor microenvironment. Specifically, virally transduced MSCs and Neural Stem Cells (NSCs) have exhibited the expression of chemotactic cytokines, interleukins, interferons, growth factors and prodrug-converting enzymes.The latter of which constitutes the technique known as gene-directed enzyme

prodrug therapy (GDEPT). This treatment method allows various non-toxic prodrugs to be converted into their active forms via non-endogenous enzymes produced by genetically modified stem cells.The aggregate of these characteristics makes GDEPT uniquely qualified to treat gliomas, medulloblastomas and other brain tumors. Another benefit of this therapy stems from the ability of MSCs to manipulate tight junctions within the blood brain barrier (BBB), temporarily inhibiting its exclusion properties and allowing for the seamless traversal of MSCs into the cortex; MSCs then utilize tumor-tropism mechanisms to infiltrate and destroy tumor cells in the brain

Another means by which stem cells can serve as therapeutic carriers is by the precise delivery of nanoparticles (NPs) bearing anti-cancer drugs and various other oncolytic mediators. NPs have long been used in the distribution of drugs used to treat cancer. However, the applicability of NPs is limited due to the lack of accurate targeting, their tendency to be internalized by a wide variety of normally function cells, and their rapid excretion from the body.62 One study analyzing the nanodrug deposits provided by MSCs internalized within mice found that NPs exhibited more accurate delivery of therapeutics in a developed orthotopic lung tumor.63 An additional study conducted using rats has demonstrated that MSCs infiltrate tumor tissue uniformly and that this infiltration leads to a more uniform distribution of a therapeutic payload. However, in the same study, they found no evidence to suggest MSCs could engage in long- distance tropism for a series of gliomas. Despite this, NPs conjugated to anti-cancer agents can be delivered into a tumor microenvironment reliably using stem cell-mediated tumor tropic delivery. Furthermore, MSCs retain their inherent ability to sense tumors and respond to chemokines following the anchoring of nanoparticles to their surface. In fact, there is no significant difference in tumor tropism between traditional MSCs and those bound to NPs. However, in the latter case, the half-life of the nanoparticle is increased exponentially

TYPES OF STEM CELL TRANSPLANT

Allogeneic Transplantation

In an allogeneic (A-loh-jeh-NAY-ik) transplant, we take healthy stem cells and give them to another person. The stem cells grow and mature into new, healthy stem cells that replace the patient's cancerous cells.The new cells come from a donor or from donated umbilical cord blood. If they're from a donor, their stem cells are harvested and then donated (given) to the person having the transplant.Before your transplant, you will have chemotherapy or a combination of chemotherapy and radiation therapy. This therapy kills the cancer cells, stops your immune system from working as it normally does, or both. We then add new stem cells to your bloodstream through a tube. The procedure is like a blood transfusion.

Types of Allogeneic Transplantation

- Unmodified Stem Cell Transplant
- T-Cell-Depleted Transplants
- Cord Blood Transplants
- Donor Lymphocyte Infusions (DLI)

Autologous Transplantation

In an autologous transplant, your own blood-forming stem cells are collected. You are then treated with high doses of chemotherapy. The high-dose treatment kills the cancer cells, but it also gets rid of the blood-producing cells that are left in your bone marrow. Afterward, the collected stem cells are put back into your bloodstream, allowing the bone marrow to produce new blood cells.

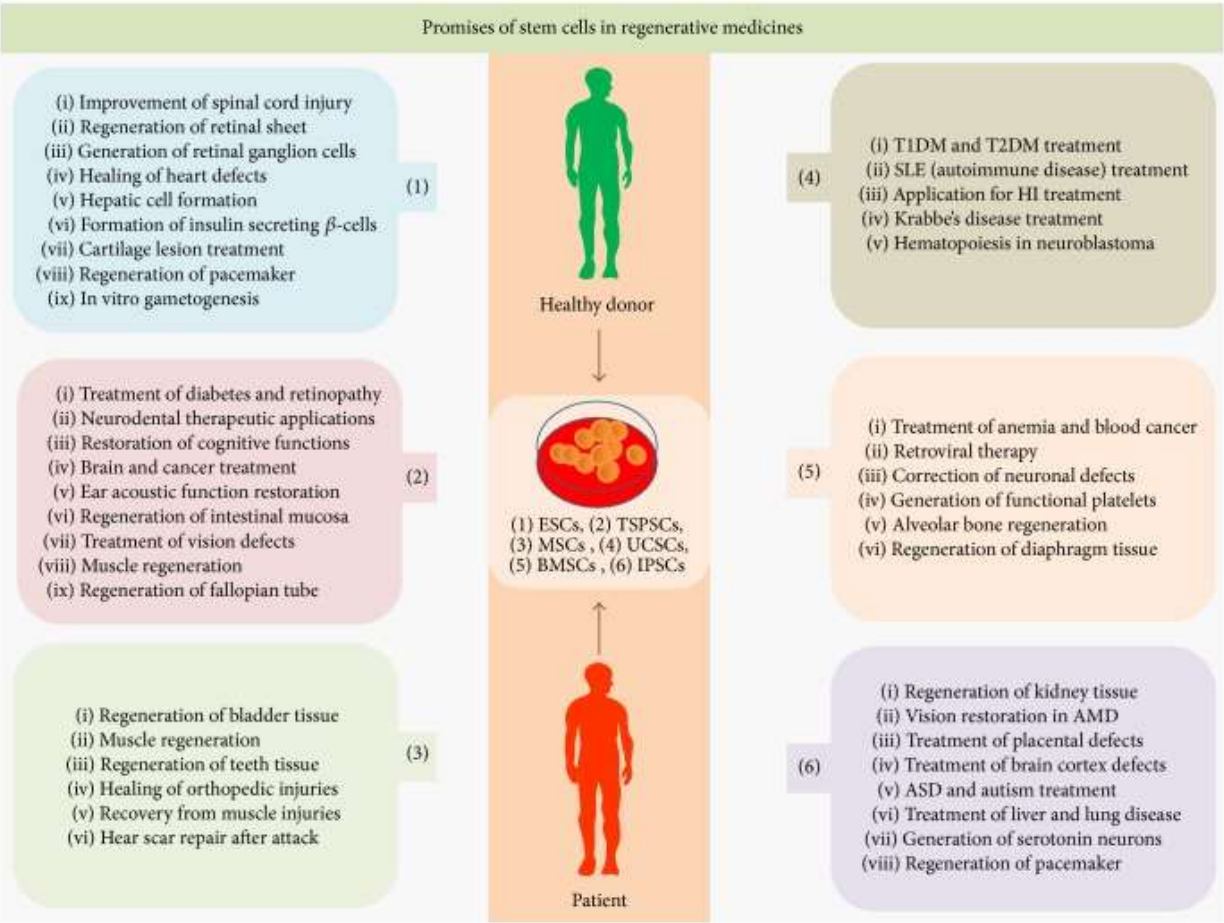

Figure 1- Promises of stem cells in regenerative medicines

Human leukocyte antigen-E (HLA-E) is a member of the group of nonclassical MHC class I molecules, also including HLA-G and HLA-F. Nonclassical MHC molecules have been especially recognized for their immunomodulatory role. Expression of HLA-G and -F is mainly restricted to specific tissues, e.g. the placenta. In contrast, expression of HLA-E is more ubiquitous and virtually every healthy cell in the body positive for HLA class I also expresses HLA-E. The molecular structure of HLA-E closely resembles that of the classical MHC class I molecules (i.e. HLA-A, -B and -C) but there are some obvious differences; HLA-E displays limited polymorphism as compared with the highly polymorphic HLA class I molecules, and thus far two dominant protein variants have been recognized. In addition, the peptide binding cleft of HLA-E allows binding of only a restricted set of peptides while classical HLA class I molecules bind a wide variety of peptides. HLA-E interacts with inhibitory and activating receptors present in NK cells and T cells, hence, having a dual function in the immune system. HLA-E has been shown to bind pathogen-derived peptides, to act as an antigen provoking an immune response in the transplantation setting and it can be aberrantly expressed by tumor cells. However, the exact influence of HLA-E on anti-viral- or anti-tumor immunity and transplantation outcome is complex and not completely known.

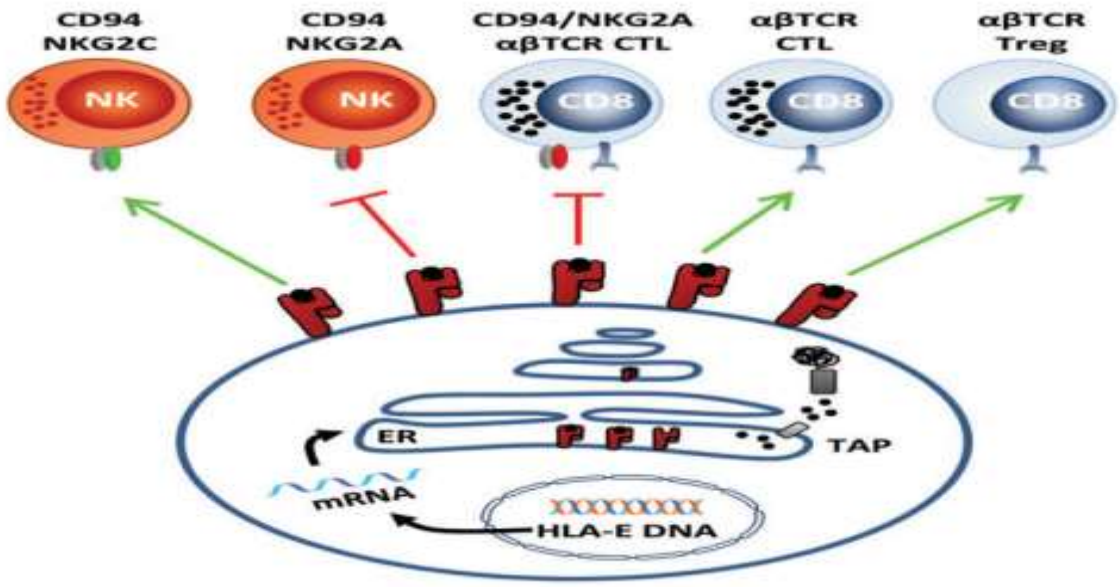

Figure 2- The activating and inhibitory effect of human leukocyte antigen-E (HLA-E) on NK cell and T cell subsets

Evidence is accumulating that HLA-E is more polymorphic and can bind a more extended peptide repertoire than initially thought. Furthermore, novel mechanisms have been identified, e.g. microRNAs, that might provide an additional explanation for aberrant expression of HLA-E during viral infection or malignant transformation. HLA-E interacts with a variety of cells leading to immune activation, upon interaction with activating receptors like the TCR on CD8 T cells or NKG2C in NK cells. Alternatively, immunosuppression will occur upon binding to inhibitory NKG2A receptors on both T cells and NK cells. Immunosuppression can also occur via the activation of HLA-E restricted regulatory T cells or upon the secretion of soluble HLA-E molecules by virally infected cells, tumor cells or accessory cells like endothelial cells.

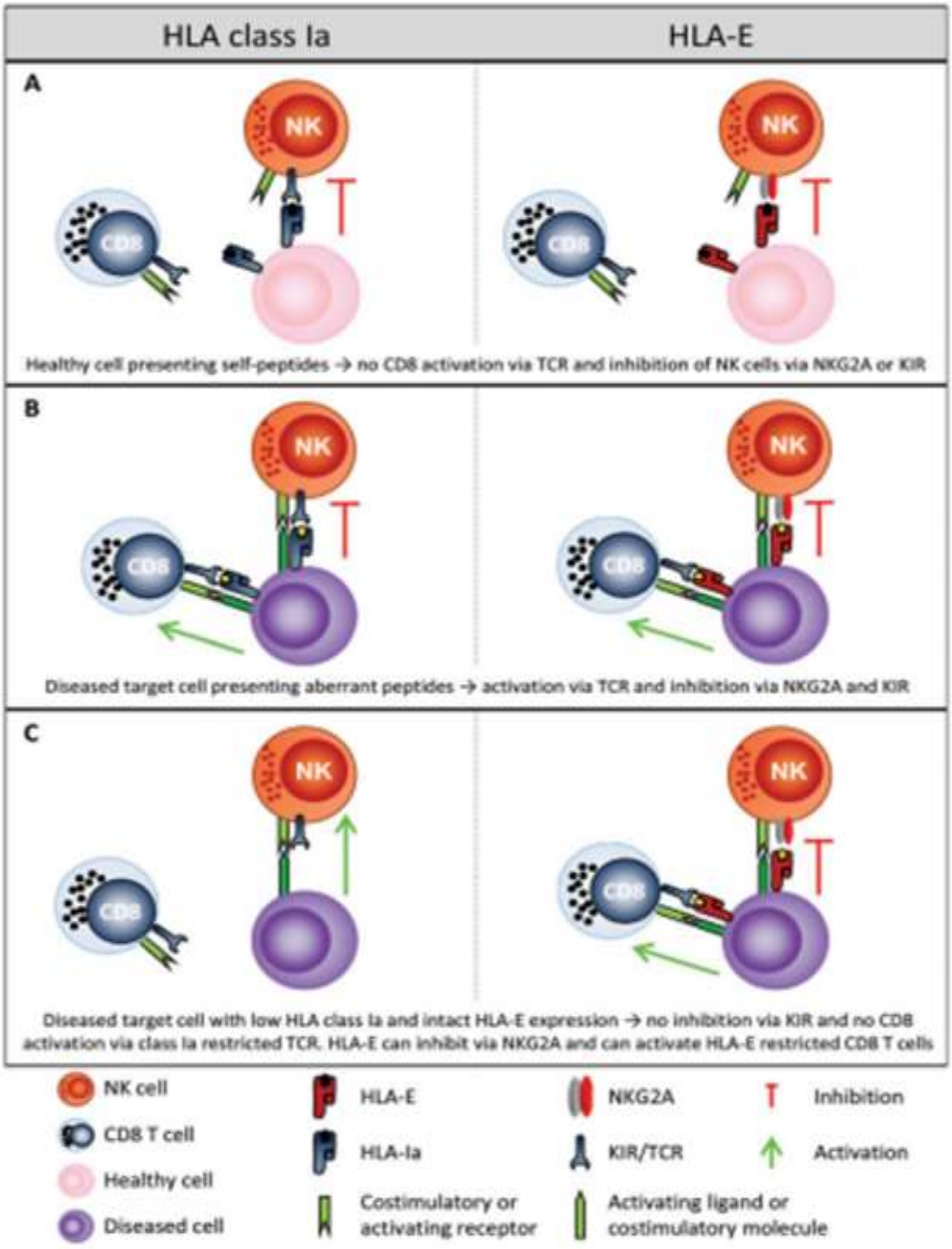

Figure 3 The effect of HLA-E on the cellular immune response in transplantation and cancer

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