

T Cells and Immunity

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ABSTRACT

T-lymphocytes or T-cells are, along with B-lymphocytes, cells of acquired immunity. They are activated upon contact with their antigen and perform a wide range of functions that include cellular immunity and regulation of the immune response.

Keywords: T-cells, B-cells, Human Immune System, Antigens, Health.

INTRODUCTION

Immune inhibition orchestrated with the aid of using a couple of negative checkpoint receptors (NCRs) is needed to manipulate aberrant immune responses and hold homeostasis [1]. An imbalance between immune activation and inhibition is assumed to be a crucial mechanism using the improvement of some illnesses. Several tumors hijack this sensitive stability and are capable of growing the expression of numerous inhibitory receptors on cytotoxic T cells (CTLs) ensuing in useless anti-tumor CTL responses. T-cell immunotherapies that block NCR signaling have proven exceptional medical achievement and make bigger median development-unfastened survival as proper as typical survival in a huge variety of cancer settings. In continual infections along with HIV and Hepatitis B and C, CTLs were determined to overexpress numerous NCRs ensuing in an “exhausted” CTL phenotype, that is related to disease development and the improvement of co-morbidities. On the other hand, the downregulation of NCRs is the idea to cause autoimmune diseases along with a couple of sclerosis and different neuroinflammatory conditions.

SYSTEMS BIOLOGY

The emergence of molecular biology has furnished exceptional development in the knowledge of the additives and the feature of organic structures [2]. We have in-depth expertise in the primary molecular-level mechanisms of an organic device, such as replication, transcription, translation, and so forth. The whole DNA series facts are to be had for human beings and plenty of different organisms as properly. A big variety of gene units and their transcriptional merchandise were identified, and superior technology is to be had to acquire tremendous gene expression

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profiles and take a look at them on the messenger RNA (mRNA) and protein levels. Although the identity of character organic additives and their feature is essential, it's miles crucial to apprehend how those organic additives interact with every different and feature as an entire device.

Systems biology is a rising discipline in biology and objectives of knowledge of the organic system as a complete device rather than its remoted parts, with the aid of using thinking about as lots of its additives as feasible, and analyzing their homes and molecular interplay networks. It makes use of the application of experimental, computational, and theoretical modeling strategies and research organic structures in maximum elements, from the molecular stage, via the cellular, and behavioral levels. Broadly, "structures biology" is described because of the quantification of the molecular factors of an organic device and integration of that facts to take a look at the organic structures and the usage of computational and statistical methods, from which hypotheses can be made in addition to investigation.

Decades of clinical research prove the involvement of the immune device in most cancers pathology and medical outcome. Cells and molecules of the immune device are essential additives of the tumor environment, and they can apprehend and remove the malignant cells with the aid of using eliciting an immune reaction in opposition to tumor-specific antigens. Encouraging observations from most cancers immunology research brought about the improvement of most cancers immunotherapy, which is a rising healing choice for the remedy of most cancers. Cancer immunotherapy complements host immunity to apprehend and remove malignant cells both with the aid of using stimulating a selected factor of the immune device or counteracting immune suppressive alerts withinside the tumor microenvironment. There were successes in growing immunotherapies utilizing immune checkpoint inhibitors, antitumor antibodies, adoptive T cell remedy, natural killer (NK) cell remedy, and dendritic cell remedy, which brought about the improvement of a couple of FDA authorized immunotherapies, inclusive of sipuleucel-T and ipilimumab.

However, tumor cells regularly withstand immune-mediated cell loss of life and set off an immunosuppressive microenvironment that favors the boom of immunosuppressive cell populations, along with regulatory T cells (Treg cells), thereby escaping from detection and

destruction with the aid of using the host immune reaction. Tumor-immunity interplay and the purposeful dynamics of the tumor microenvironment are complicated; therefore, it highlights the requirement of structures biology-primarily based methods to characterize the tumor microenvironment and growing techniques for most cancers remedy. Systems biology methods offer several packages to the discipline of most cancers biology inclusive of screening and identity of capacity biomarkers for the analysis and prognosis of illnesses; elucidation of the organic pathways related to the sickness pathology and medical outcome; the identity of the healing goals and knowledge their mode of action; evaluation of drug efficacy; the identity of sufferers' subpopulation primarily based totally on their reaction to the remedy; and prediction of the drug toxicity. Overall, structures biology garners large interest and has been applied significantly in most cancer studies in current times.

HUMAN IMMUNE SYSTEM

The human immune device employs some mechanisms for preserving stability among immune activation and suppression [1]. Infection, cancers, and damage trigger inflammatory techniques that want to be "checked" to keep away from aberrant responses. This complicated system entails a couple of cellular components that must paintings in live performance to reap the ideal stage of inflammation. Under homeostatic conditions, immune cells are designed so that they're now no longer constitutively lively which can cause harm to wholesome tissues or sickness. One of the methods wherein the immune device moderates this stability is via the binding of ligands on antigen-offering cells (APCs) to corresponding poor immune checkpoint receptors (NCRs) on T cells. Specifically, those immune checkpoints are proteins that act as T cellular receptor (TCR) co-signaling companions that supply both fantastic or poor alerts to T lymphocytes. Ligand binding outcomes in down law of T cell activation and suppression of effector capabilities. However, in lots of sickness states, this device is hijacked, therefore main to T cell disorder and useless responses. Chronic contamination and cancers were proven to do simply that.

Much attempt has been made in the direction of higher knowledge of those NCRs and the position they play in health and sickness. Moreover, figuring out methods wherein those NCRs may be blocked to repair effector features and higher function T cells to combat cancerous tumors and infections

has been a major focus of studies. Harnessing this device to decorate the T cell feature has been groundbreaking for the sphere of immunology, a lot so that the 2018 Nobel prize in physiology and medicine went to the 2 men who observed those crucial immune molecules, James Allison and Tasuku Honjo. The concept of mobilizing our immune structures to combat sickness isn't always a brand-new concept. However, the invention of those immune-modulatory receptors has made this tantalizing opportunity possible as a promising medical remedy. Among the maximum outstanding immune checkpoint, receptor-ligand combos are CTLA-4/CD80, PD-1/PD-L1, TIGIT/PVR, and Tim-3/Galectin 9.

FUNCTIONS

T cells are the subset of lymphocytes that broaden withinside the thymus [3]. They are in addition delineated with the aid of using the expression of cell surface markers and the manufacturing of inflammatory and immunoregulatory mediators. Two T cell subsets, CD8⁺, and CD4⁺ T cells are activated thru the reputation of peptides derived from the antigen. For activation of T cells to arise, the peptides are certain to be essential histocompatibility complexes (MHCs) expressed at the floor of specialized white blood cells referred to as antigen-offering cells. T cells have numerous capabilities withinside the immune reaction.

CD8⁺ T cells are activated in reaction to antigens that benefit get right of entry to the cytosol of cells. These antigens are damaged down into peptides. The peptides are supplied to CD8⁺ T cells after being certain to magnificence I MHC molecules. Class I MHC molecules are expressed on almost all nucleated cells. CD8⁺ T cells explicitly have a T cellular receptor (TCR) that binds peptide-magnificence I MHC complexes. CD8⁺ T cells that explicit one-of-a-kind TCRs permit the reputation of many one-of-a-kind antigens. The binding of the CD8⁺ T cell TCR to the peptide-magnificence I MHC complicated on expert antigen-offering cells (e.g., dendritic cells) turns on the CD8⁺ T cells which then reply in opposition to cytosolic infections along with viruses, intracytoplasmic bacteria, and protozoa. Activated CD8⁺ T cells set off the loss of life of inflamed cells via mechanisms that include (1) the launch of granules containing the pore-forming molecular perforin or (2) the engagement of Fas receptors on track cells. Both mechanisms set off apoptosis, or programmed cell death, withinside the goal cell. In addition, activated CD8⁺ T cells secrete cytokines, molecules

crucial to intercellular communication, that recruit and prompt macrophages and neutrophils.

In comparison to CD8⁺ T cells, CD4⁺ T cells are predominantly activated in reaction to extracellular antigens which can be endocytosed or phagocytosed, damaged down into peptides, and certain to magnificence II MHC molecules on the floor of expert antigen-offering cells. Class II MHC molecules are expressed on dendritic cells, macrophages, B cells, and activated T cells. The CD4⁺ T cells explicit TCRs that bind peptide-magnificence II MHC complexes. Recognition of peptide antigen-MHC complexes turns on CD4⁺ T cells in opposition to loads of antigens inclusive of, however now no longer confined to, bacteria, parasites, and proteins. Activated CD4⁺ T cells direct elements of the immune reaction thru the secretion of immunoregulatory cytokines and different soluble mediators. These inflammatory mediators can set off B cells to go through immunoglobulin (Ig) magnificence switching (e.g., IgM to IgE); to assist the pastime of CD8⁺ T cells; to recruit and prompt eosinophils, basophils, neutrophils, mast cells, and macrophages; and to down-adjust immune responses. Several lineages of CD4⁺ T cells, with overlapping and competing consequences primarily based totally on the ones defined above, were identified. One CD4⁺ T cell lineage referred to as regulatory T cells, has capabilities to hold self-tolerance and immune homeostasis. In addition, a few CD4⁺ T cells can set off cytolysis thru the mechanisms defined for CD8⁺ T cells.

B lymphocytes (B cells) and T lymphocytes (T cells) are essential cellular additives of the adaptive immune device [4]. These cells can apprehend antigens specifically, which takes place via their unique receptors. B and T Lymphocytes gift as one-of-a-kind and awesome clones, which might be the populace of cells that explicitly the equal receptor with comparable specificity, and every clone is precise. Lymphocytes differentiate withinside the number one lymphoid organs, and they flow into withinside the blood and lymphoid organs even as they mature. However, they took into consideration naïve cells earlier than an antigen stumbles upon. After the reputation of their unique antigen, which they explicitly the unique receptor in opposition to, those cells go through numerous adjustments via sign transduction and intracellular signaling pathways, and they grow to be effector lymphocytes. The unique receptor at the floor of B cellular is referred to as B cell receptor (BCR),

which is equal to an antibody molecule but has a membrane-certain shape of it. T cell receptor (TCR) is the unique receptor expressed on the floor of a T cell. Both BCR and TCR molecules have clonal differentiation and distribution. A crucial feature of TCR and BCR molecules is their diversity.

If a few thresholds of contamination are surpassed and the innate immune device isn't always capable of cleaning the contamination, the adaptive immune reaction is triggered [5]. Triggering of the adaptive immune reaction relies upon the shipping of the infectious agent to the lymphoid organs, along with a lymph node, then reputation and proliferation with the aid of using the naive T and naive B cells located there. The antigen-offering cell, along with a mature dendritic cell, grabs the antigen at the site of contamination and migrates with it to the nearby lymphoid organ that includes naive T and naive B cells. The dendritic cell then offers the antigen to the naive T cell. The naive T-cell will become unique effector cells that multiply. They grow to be both antigen-unique CD8 cytotoxic T cells or antigen-unique helper CD4 T cells. Some of the armed effector T cells, in particular the cytotoxic T cells, go away from the lymphoid tissue following the chemokine path and returned to the page of contamination to kill the pathogens. Some of the effector T cells, in particular the antigen-unique helper T cells, live in the lymphoid tissue to assist prompt B cells which can be offering the unique antigen on their cellular membranes. Antigen-unique B cells commonly do now no longer get to paintings till they stumble upon antigen-unique helper T cells. The B cells grow exponentially for more than one day and grow to be the antibody-generating plasma cells. It takes approximately 4 days for the adaptive immune device to broaden a unique reaction the primary time an infectious agent invades a person.

Once contamination is cleared, a maximum of the effector cells die, and a selected immunological reminiscence is retained in reminiscence T and reminiscence B cells. Memory T cells final a very lengthy time, truly forever, and are answerable for the lengthy-time period of safety after contamination or immunization. The second time the pathogen infects a person, the unique reminiscence T and B cells produce a miles extra speedy and stronger reaction. Antigen-unique reminiscence B cells reflect and convey antibodies with better affinity, this is, better binding power for its antigen, than the number one reaction.

CAR

The genetic engineering of T cells with a chimeric antigen receptor (CAR) allows adoptively transferred T cells to apprehend unique tumor goals [6]. These synthetic receptors have a shape this is analogous to the canonical additives that are important for T-cell signaling. CARs have an antigen-binding domain, the single chain variable fragment (scFV), which includes the immunoglobulin VH and VL. The CD3 zeta chain mediates the activating belongings of CARs, whereas the costimulatory homes are performed with the aid of using co-receptors along with CD28 and 4-1BB. Hence, the CAR mediates antigen reputation, T-cell activation, and costimulation. Of note, CARs are awesome from physiologic T-cell receptors in that those molecules do now no longer want peptide processing or HLA expression for antigen binding. CAR T-cell engineering has advanced over the years and there is now merchandise that can be denoted as fourth technology CAR T cells. This CART-cellular merchandise might also additionally make use of costimulatory receptors, along with CD28, 4-1BB, CD134, or CD137. Of note, the fourth technology CARs are the maximum novel generation and use a website called TRUCK or T-cell Redirected to Universal Cytokine Killing. This unique technology is supported with the aid of using activated T-cellular nuclear transcriptional alerts, which lets them secrete unique cytokines such as IL-12 into the tumor microenvironment. This signaling additionally aids withinside the recruitment and activation of different immune cells to make certain a sturdy immune reaction.

Ongoing studies with CAR T cells are targeted on techniques to (1) enhance CAR T-cell persistence, (2) lower antigen loss as a mechanism of sickness relapse, (3) broaden CARs for a wider variety of hematologic malignancies in addition to strong tumors and, (4) lower fees of the remedy. Along with the changes to the engineering of the CAR assemble and upgrades to the domain names of the receptor, CRISPR/Cas9 enhancement of the CAR has begun to in addition enhance signaling of the CAR. The CRISPR/Cas9 device has been hired to goal the genes of inhibitory receptors, along with PD-1, Fas, and HLA-I, to concurrently delete those genes and restrict protein expression of those immune device inhibitors at the CAR itself. Pre-medical in vivo and in vitro research with the Fas/HLA-I/CD3 triple deletion CAR have proven that this approach lets in for accelerated CAR persistence and

more desirable immunologic pastime with stepped forward cytotoxicity and cytokine secretion from the CAR T cells. Dual concentrated on techniques for CAR T cell objectives to lower the capacity for relapse because of antigen loss with the aid of using concurrently concentrated on a couple of antigens, along with CD19 and CD22. Investigators are actively running to analyze capacity antigens to efficaciously deal with illnesses starting from AML and pancreatic cancers. Finally, others also are utilizing CRISPR/Cas9 to broaden off-the-shelf CAR T-cell treatments which can lower the fees wished for the technology of personalized CAR T cells.

NEUROINFLAMMATION

The antigen is taken up with the aid of using antigen-offering mononuclear phagocytes (MP) along with macrophages, dendritic cells, or microglia, processed, after which supplied to cells of the adaptive immune device producing an effective, sturdy, and unique immune reaction [7]. Because of this, antigen-offering cells (APCs) are the bridge between innate and adaptive immune devices. They without delay prompt T cells at some stage in antigen presentation, inflicting them to proliferate and migrate to regions of damage or contamination. Specifically, APCs prompt T cells via the presentation of antigens alongside essential histocompatibility complicated (MHC) molecules and interplay with T cell receptors (TCRs) and co-stimulatory molecules such as CD80, CD86, CD70, CD40, and CD200. Because of the capacity to apprehend unique antigens, T cells contain the cellular populace this is answerable for precise immune specificity. Once activated, T cells go through clonal growth to grow their cellular variety and capacity to remove pathogens. Such activation reasons T cell differentiation, growth, and proliferation with related cytokine manufacturing inside a surrounding environment. Likewise, APCs themselves supply many cytokine alerts inclusive of IL-12, IL-4, IL-6, and remodeling boom thing beta (TGF- β) to polarize naïve T cells into activated T cells with unique effector capabilities.

There are essential T cell subsets that may be generated from each lymphoid tissue along with the thymus, spleen, and lymph node, or withinside the periphery. Upon activation with the aid of using innate immunity, CD4⁺ T cells differentiate into one-of-a-kind subsets along with T helper 1 (Th1), Th2, Th17, and regulatory T cells (Tregs). Classically, Th1 and Th17 cells mount lively immune responses via the secretion of proinflammatory cytokines and mediators, inclusive of

interferon-gamma (IFN- γ) and IL-17A. On the alternative hand, Th2 and Tregs are answerable for anti-inflammatory responses. Specifically, Tregs hold suppression of an immune reaction. Tregs mediate this feature with the aid of using diminishing antigen presentation and secreting anti-inflammatory cytokines inclusive of IL-10, IL-35, and TGF- β . These cause suppression of activated MP and T effector cells (Teffs). Each of those T cell subsets plays essential but impartial roles in mounting a sturdy and effective adaptive immune reaction. Following activation, T cells are recruited to sites of sickness and cell inflammation. To input sites of sickness, cells go through extravasation. This system lets circulating lymphocytes emigrate across cellular obstacles along with the BBB to benefit access to sites of inflammation. Once withinside the brain, cell-mediated immune responses can affect neurodegeneration. The cross-communicate among T cells and glia mediate effector capabilities with the aid of using both cell-cell touch or cytokine-mediated mechanisms, inclusive of direct cytotoxicity with the aid of using proinflammatory cytokines, activation of microglia or faded suppressive feature of Tregs.

This interaction between the innate and adaptive immune fingers is important for the improvement of neuroinflammation because it influences neurodegeneration or neuroprotection. Findings from a couple of neurological problems have provided perception into not unusual place sickness outcomes. Although neuroinflammation and T cell interactions play an outstanding position in sickness development or safety in opposition to sickness, it has to be noted that the sort of immune reaction is usually unique.

ANTIGEN PROCESSING

The idea of antigen processing has emerged from the need to explain a hard and fast of experimental findings displaying that T cells can apprehend denatured antigens simply in addition to local proteins, and small peptide fragments similarly properly because of the complete protein [8]. These observations counseled that the antigenicity of proteins for T cells could lie withinside the number one amino acid series, in comparison to B-cell epitopes that are regarded to rely upon the secondary/tertiary shape of proteins. Provided that T cells apprehend brief amino acid sequences, local proteins ought to only be diagnosed similarly properly, if the immunogenic sequences have been located completely at the protein floor. This speculation could expect that, at least in a

few instances, while the protein floor lacks T-cell epitopes, the complete local protein has to be nonimmunogenic for T cells. However, this becomes now no longer discovered in reality. Therefore, an opportunity idea become introduced providing that local proteins could now no longer be diagnosed with the aid of using T cells at all, earlier than they became 'processed', i.e., damaged down into brief peptides. Under this speculation, processing becomes taken into consideration to be a compulsory step taking place at some stage in the time that elapsed among the management of antigen and the T-cell reputation event.

Dendritic cells are determined at numerous places withinside the frame, inclusive of the blood, afferent lymph, and lymphoid organs in addition to the interstitium of maximum non-lymphoid organs (except the brain). They might also additionally have one-of-a-kind names, e.g., pores and skin dendritic cells are termed Langerhans cells, and the ones withinside the afferent lymph-veiled cells, and withinside the lymphoid organs, they're called interdigitating cells. Organ-resident dendritic cells absorb antigens very efficaciously and synthesize MHC molecules concurrently. After antigen uptake, they prevent MHC synthesis, thereby freezing the antigenic spectrum supplied, and migrating thru afferent lymph to the T-dependent regions of lymphoid organs. The antigens continue to be immunogenic on their floor for a protracted time (at least 1–2 days). The positioning of dendritic cells forces recirculating T cells to leave the bloodstream at this vicinity to satisfy antigen, and for this reason, optimizes the risk of locating T cells unique for the supplied antigens. The priming of naive T cells appears to arise at those places. In addition to antigen presentation, dendritic cells additionally can shape strong clusters with antigen-unique T cells facilitating thereby the priming system. It is likewise feasible that they offer extra to-date unknown 'alerts' or 'elements' vital for priming. Once primed, T cells redistribute once more withinside the frame, exercising their effector feature on numerous styles of cells sporting equal antigens.

IMMUNOTHERAPY

Immunotherapy boosts the immune responses in opposition to cancers with the aid of using supplying primed T cells both in vivo and ex vivo [9]. Therapeutic most cancers vaccines offer the possibility to high the T cells in vivo, even as adoptive T-cell switch items ex vivo primed T cells to

the immune device of most cancers sufferers. DC vaccines represent the maximum famous healing of most cancers vaccines evolved to deal with a huge range of cancers. First, DCs have to be cultured from sufferers' peripheral blood mononuclear cells (PBMCs). Then they have to be matured (maximum usually with inflammatory cytokine cocktails) and loaded with tumor antigens. Finally, they are reintroduced to the patient's frame to prompt T cells and decorate antitumor responses. Some researchers select in vivo maturation of DCs with the aid of using an injection of those cells into an infamed tissue as a simple, inexpensive, and physiologic manner of maturation that complements the migration of DCs to draining lymph nodes. Furthermore, antigens also can be loaded in vivo with the usage of antibodies that bind DC floor like DEC205. DC vaccines are below investigation (section I/II medical trial) for high-grade glioma, glioblastoma, hepatocellular carcinoma, pancreatic cancer, colorectal cancer, metastatic melanoma, a couple of myelomas, acute leukemia, breast cancer, ovarian cancer, RCC, and non-small cell lung cancer. On the alternative hand, the adoptive T-cell switch is predicated on in vitro growth of T cells harvested from most cancer sufferers and the reintroduction of those manipulated and primed T cells into the patient's circulation. These T cells may be harvested from 4 major sites: (1) PBMC, (2) resections from draining lymph nodes, (3) malignant effusions, and (4) without delay from tumor biopsies. However, the amount and fine of harvested T cells from every site differ significantly; PBMCs are a clean site to acquire T cells, even as biopsy-derived T cells are extra reactive in opposition to tumor antigens. Thereafter, T cells will be engineered to explicit T-cell receptors (TCR) vital for tumor reputation or to explicit T bodies (a chimeric antigen receptor that without delay binds tumor antigens). Finally, T cells may be accelerated with publicity to applicable tumor antigens, activating mAbs and T-cell boom elements like IL-15. CD8⁺ cytotoxic T lymphocytes represent the primary cells produced and transferred in adoptive T-cell remedy. The adoptive T-cell remedy is now underway for neuroblastoma, hepatocellular cancers, gastric most cancers, metastatic melanoma, hematological malignancies, colorectal most cancers, posttransplant lymphoproliferative illnesses, breast most cancers, ovarian most cancers, superior lung most cancers, RCC, and nasopharyngeal carcinoma. Recently, an HLA-impartial concentrated on most cancer cells, that is directed with the aid of using nonconventional T cells, has

been reported. It has been discovered that a few ligands with the aid of using most cancer cells gift at the monomorphic MHC class 1-related protein (MR1) and are diagnosed with the aid of using nonconventional T cells. MR1, with confined polymorphism, is an excellent candidate for designing immunotherapeutics for nearly all sufferers. Moreover, the TCR answerable for this reputation can be followed with the aid of using T cells from sufferers with numerous styles of most cancers, which ends up in more desirable cytotoxicity in opposition to the installed tumor. This technique confirmed promising outcomes withinside the destruction of autologous and allogeneic melanoma.

CONCLUSION

As constituents of the blood, lymphocytes are the smallest cells that have a defensive role. They produce antibodies and participate in the immune system in various ways. They are part of leukocytes and are produced in the bone marrow. In adults, lymphocytes make up 25-40 percent of leukocytes in the blood. Three basic groups of lymphocytes do not differ morphologically, but the differences are only functional: B-lymphocytes, T-lymphocytes, and NK-cells, which are the least known and are thought to be responsible for preventing the proliferation of abnormal cells, especially tumor cells.

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