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T-cell receptor family, signal transduction, and transcription factors in T-cell immune response

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ABSTRACT

This study investigated signal transduction in T-lymphocytes, whose cell receptors are categorized into several groups based on their signaling mechanisms and the intracellular biochemical pathways they activate, including modular signaling proteins and adapter molecules that perform scaffolding or catalytic functions. Adapter proteins facilitate signaling complexes by linking various enzymes. Immune receptors, which are composed of integral membrane proteins from the immunoglobulin superfamily, interact with specific tyrosine-containing motifs within transmembrane signaling proteins in their cytoplasmic domains. The intensity of T-cell receptor signaling influences the development and activation of T-lymphocytes. Signal transduction is regulated by coreceptor activation and suppressed by inhibitory receptors. The interaction between T-cell receptors and major histocompatibility complex molecules induces coreceptor clustering and tyrosine phosphorylation of immunoreceptor tyrosine-based activation motifs within the cluster of differentiation 3 complex. Protein and lipid phosphorylation is a key regulatory mechanism in T-cell receptor and coreceptor signaling. Activated zeta-chain-associated protein kinase 70 phosphorylates adapter proteins, promoting interactions with downstream signaling molecules. G-proteins stimulate mitogen-activated protein kinases, which activate transcription factors. Phospholipase C activates T-cell transcription factors, resulting in enhanced gene transcription. T-cell receptor signal modulation is mediated by protein tyrosine phosphatases, which dephosphorylate tyrosine residues on signaling proteins, inhibiting T-cell receptor-mediated signal transduction.

Keywords: kinases; receptors; signaling molecules; major histocompatibility complex; coreceptor clustering; T-lymphocytes; transcription factors; phosphorylation.

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Семейство Т-клеточных рецепторов, сигнальная трансдукция и транскрипционные факторы Т-клеточного иммунного ответа

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АННОТАЦИЯ
Рассматривается передача сигналов Т-лимфоцитами, клеточные рецепторы которых сгруппированы в несколько категорий по используемым сигнальным механизмам и активируемым ими внутриклеточным биохимическим путям, в частности модульные сигнальные белки, адаптеры, выполняющие связующую или каталитическую функции. Адаптерные белки связывают различные ферменты, способствующие сборке комплексов сигнальных молекул. Иммунные рецепторы, состоящие из интегральных мембранных белков суперсемейства иммуноглобулинов, взаимодействуют в цитоплазматических участках со специфическими тирозинсодержащими мотивами трансмембранных сигнальных белков. Интенсивность передачи сигналов Т-клеточными рецепторами влияет на развитие и активацию Т-лимфоцитов. Передача сигналов модулируется повышенной активацией корецепторов, модуляцией передачи сигналов супрессорными рецепторами. Взаимодействие Т-клеточного рецептора с молекулами главного комплекса гистосовместимости приводит к кластеризации корецепторов и фосфорилированию остатков мотива активации иммунорецепторов на основе тирозина в кластере дифференциации 3. Фосфорилирование белков и липидов играет центральную роль в передаче сигналов от комплекса Т-клеточного рецептора и корецепторов. Активированная протеинкиназа, ассоциированная с дзета-цепью 70, фосфорилирует адаптерные белки и способствует связыванию с сигнальными молекулами. G-белки стимулируют митоген-активируемые протеин-киназы, активирующие факторы транскрипции. Фосфолипаза С активирует факторы транскрипции Т-клеток, что приводит к усилению транскрипции их генов. Модуляция передачи сигналов Т-клеток осуществляется протеинтирозинфосфатазами, удаляющими фосфатные фрагменты из остатков тирозина белков и в целом ингибирующими передачу сигналов Т-клеточным рецептором.

Ключевые слова: киназы; рецепторы; сигнальные молекулы; главный комплекс гистосовместимости; кластеризация корецепторов; Т-лимфоциты; транскрипционные факторы; фосфорилирование.

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BACKGROUND

In a very short period of history, immunology has been enriched with important information about the characteristics of cytokines, regulatory T-cells, subsets of T helper cells, and subsets of immunocompetent cells (ICCs). This data has dramatically changed our understanding of the immune response. However, the effectiveness of both innate and adaptive immune responses depends on the structures of immune cell receptors that recognize antigens. The receptors are molecules that enable the transduction of activation signals to the ICCs. They influence the transformation of ICCs, possible immune system dysfunctions, secondary immunodeficiencies, and the development of infectious processes. Therefore, in our opinion, it would be interesting and vital to summarize information on the contribution of these molecules to the recognition of varied antigens and immune signaling pathways that affect the effectiveness and purpose of the immune response.

This work studied the Russian and international literature on the characteristics of T-cell receptors, signaling molecules, and pathways that ensure a proper immune response.

We reviewed current available Russian and international literature from 2012 to 2024 on the biological characteristics of T-cell receptors, signaling molecules, and pathways that ensure the development of immune response. The literature was searched from May 2023 to July 2024, primarily from the PubMed database using several keyword combinations: *внутриклеточная передача сигналов, ведущая к активации клеток* (*intracellular signaling leading to cell activation*), *ядерная транслокация факторов транскрипции* (*nuclear translocation of transcription factors*), *рецепторы антигенов на Т-лимфоцитах* (*antigen receptors on T-lymphocytes*), *рецептор тирозинкиназы* (*receptor tyrosine kinase*), *внутриклеточные биохимические пути* (*intracellular biochemical pathways that they activate*). The results were manually filtered, reviewed, and discussed by all authors of this article.

Interest in this problem was initially shown by Paul Ehrlich, who predicted that specific cell surface receptors induce intracellular signaling, intercellular adhesion, and the internalization of extracellular molecules. Most plasma membrane receptors initiate signaling after modification by enzymes that activate transcription factors [1]. In the nuclear phase, these transcription factors bind to the target DNA and induce changes in gene expression patterns. Signal transduction is associated with stimulating cell motility, granular exocytosis, and gene expression. It can either induce cell differentiation, proliferation, and apoptosis, or prevent cell cycle arrest and death [2].

Signal receptors are integral plasma membrane proteins; their extracellular domains recognize soluble secreted ligands or interact with similar structures anchored within the plasma membrane of an adjacent cell or with the extracellular matrix. Nuclear receptors are intracellular (cytosolic, nuclear) transcription factors that are activated by lipid-soluble ligands. Receptor signaling requires the ligand-induced clustering of receptor proteins (cross-linking), associated with conformational and structural changes within the cytosolic domain of the nuclear receptor, which facilitate recruitment and interaction with other signaling molecules [3].

The enzymatic phosphorylation of the amino acid side chains within the cytosolic portion of a receptor is an early signaling event. Serine/threonine and lipid kinases phosphorylate their respective substrates and thus participate in various signaling pathways. Specific phosphatases catalyze the dephosphorylation of these amino acids and inhibit signaling [4]. Protein phosphorylation and the covalent binding of ubiquitin molecules via the post-translational modifications of signaling components occur within the ICCs. The N-terminal regions of histones can be acetylated and methylated to modulate gene expression as well as DNA replication and recombination. Non-receptor tyrosine kinases (NRTKs) are employed by integrins as well as cytokine and adhesion receptors for signal transduction and antigen recognition; they are also used by the F_c fragments of antibodies [5–7]. Receptor tyrosine kinases (RTKs) self-activate the cytoplasmic domains of the receptors but do not play any crucial role in lymphocyte activation. Examples of RTKs include the c-*KIT* protein; *c-kit* mutants demonstrate abnormal cell signaling and proliferation. Insulin, epidermal, and platelet-derived growth factor receptors are included within RTKs [8–9].

Nuclear receptors stimulate or suppress gene transcription. G-protein-coupled receptors (GPCRs) activate the respective guanosine triphosphate (GTP)-binding proteins. They span the plasma membrane seven times and are called serpentine or seven-transmembrane GPCRs. They include the receptors for leukotrienes, prostaglandins, histamine, complement components, bacterial formyl peptides, sphingosine-L-phosphate, and chemokines. The varied types of GPCR-associated G proteins exhibit activating or inhibitory effects. For example, the Notch family of proteins regulates lymphocyte development and influences mature lymphocyte activation. The WNT proteins participate in lymphopoiesis, enhance β-catenin levels, and activate transcription factors that promote B and T-cell development [10, 11]. The modular

structures of tyrosine kinases belonging to various families play important roles in immune responses (Fig. 1).

NRTKs of the SRC family contain SRC homology 2 (SH2) and SH3 homologous domains that mediate binding with signaling proteins. The Rous sarcoma virus protein (c-SRC) also comprises catalytic tyrosine kinase and N-terminal lipid attachment domains; the latter facilitates covalent bonding with a myristic acid molecule. Myristate promotes the attachment of SRC kinases to the plasma membrane. The SH2 domains consist of ~100 amino acids and are conformationally folded to allow binding to the phosphotyrosine-containing regions of proteins; e.g., in spleen tyrosine kinases (SYKs) and Zeta-chain-associated protein kinase 70 (ZAP70) (Fig. 1). The recruitment of SYKs and ZAP70 to the antigen-recognizing receptor is crucial for antigen-induced lymphocyte activation. Similarly, ~100 amino acids of the SH3 domains mediate

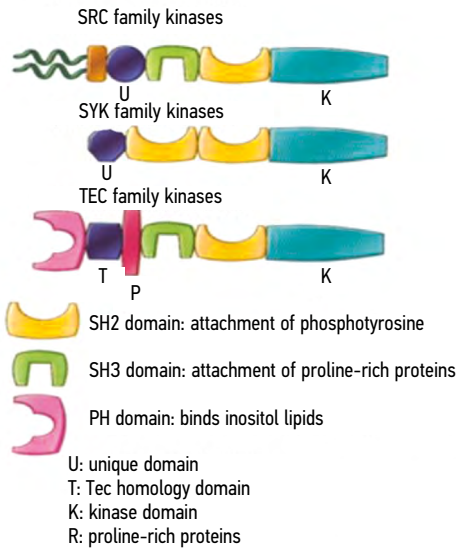

Fig. 1. Modular structure of tyrosine kinases affecting lymphocyte activation: PH — pleckstrin homology domain; SH — SRC homology domain (adapted from [19] A.K. Abbas et al., 2022. Distributed under the terms of the CC-BY 4.0 license)
Рис. 1. Модульная структура тирозинкиназ, влияющих на активацию лимфоцитов: PH — домен гомолога плекстрина; SH — домен гомолога SRC (адаптировано из [19] A.K. Abbas и соавт., 2022. Распространяется на условиях лицензии CC-BY 4.0)

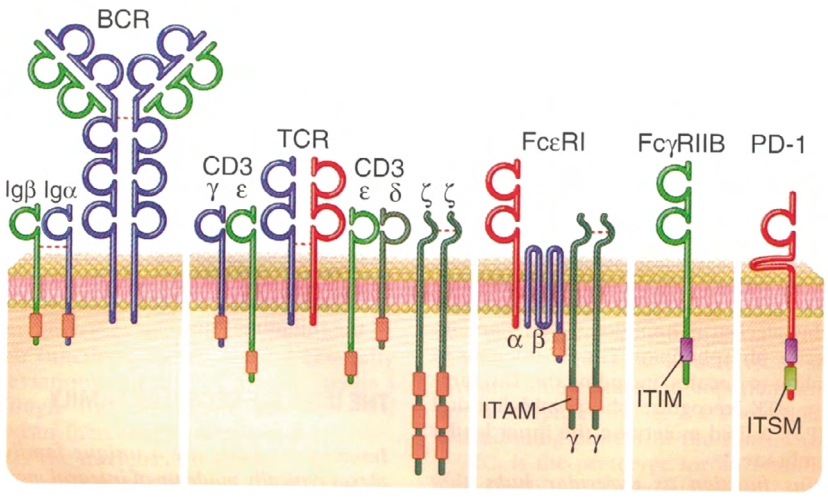

Fig. 2. Individual members of the immune receptor family: BCR — B-cell receptor; TCR — T-cell receptor; FcεRI — high-affinity IgE receptor; FcγRIIB — unique inhibitory IgG receptor; PD-1 — programmed cell death protein-1; ITAM — immunoreceptor tyrosine-based activation motif; ITIM — immunoreceptor tyrosine-based inhibitory motif; ITSM — immunoreceptor tyrosine-based switch motif (adapted from [19] A.K. Abbas et al., 2022. Distributed under the terms of the CC-BY 4.0 license)
Рис. 2. Отдельные представители семейства иммунных рецепторов: BCR — B-клеточный рецептор; TCR — T-клеточный рецептор; FcεRI — высокоаффинный IgE-рецептор; FcγRIIB — уникальный ингибирующий IgG-рецептор; PD-1 — белок запрограммированной клеточной гибели-1; ITAM — иммунорецепторный мотив активации на основе тирозина; ITIM — иммунорецепторный ингибирующий мотив на основе тирозина; ITSM — иммунорецепторный мотив переключения на основе тирозина (адаптировано из [19] A.K. Abbas и соавт., 2022. Распространяется на условиях лицензии CC-BY 4.0)

protein–protein interactions (PPIs) by binding to the proline-rich regions of unphosphorylated proteins. The Pleckstrin homology (PH) and TEC family of tyrosine kinases recognize phospholipids and phosphatidylinositol trisphosphate (PIP3, a moiety on the inner surface of the plasma membrane), respectively [12–14].

A broad group of adapter proteins, LAT, B cell linker (BLNK), SH2 domain-containing leukocyte protein of 76 kDa (SLP76), and Grb2-related adapter downstream of Shc (GADS), plays an important role in signaling, which facilitates the formation of large signaling complexes. These adapters contain SH2 and SH3 domains, which mediate PPIs and docking with other signaling molecules. Tyrosine kinase binds specifically with the SH2 domain of phosphoinositide 3-kinase (PI3-kinase). Tyrosine phosphorylation induces PPIs and activates specific enzymes that affect nuclear localization and the activities of specific downstream transcription factors. Clustering of phase-separated proteins is a fundamental mechanism underlying signal transduction and transcription. It includes the assembly of adapters into complexes after T-cell receptor (TCR) signaling, the activation of cytosolic receptors, and inflammasome formation. The activation of these receptors induces an antiviral immune response and autoimmune reactions [15–17]. Immune receptors are a unique family of receptor complexes that usually consist of integral membrane proteins of the immunoglobulin (Ig) superfamily involved in recognizing ligands bound to other transmembrane signaling proteins. These proteins have unique tyrosine-containing motifs within their cytoplasmic domains (Fig. 2) [18].

The individual members of the receptor family comprise a single chain where the extracellular domain recognizes ligands and the cytoplasmic domain contains tyrosine residues that facilitate signal transduction. These cytoplasmic tyrosine-containing motifs of signaling proteins are classified into three types: activating, inhibitory, and activating or inhibitory, depending on the cell type and the specific immune receptor (Fig. 2). Signaling proteins are located near the SRC family of tyrosine kinases. These phosphorylate the immunoreceptor tyrosine-based activation motifs (ITAMs), which further recruit SYKs or ZAP70, which contain tandem SH2 domains. These domains bind to one of the two phosphorylated ITAMs, thus causing conformational changes that activate the kinase and induce processes that control ICC activation. The signaling pathways associated with certain immune receptors that contain immunoreceptor tyrosine-based inhibition motifs (ITIMs) suppress cellular responses. ITIMs recruit tyrosine phosphatases and counteract the ITAM-based activation of immune receptors [19–21].

Other receptors contain an immunoreceptor tyrosine-based switch motif (ITSM) that functions as an inhibitor and an SH2-recruiting domain. Within signaling lymphocytic activation molecules (SLAMs), this motif controls the switching of the binding domain-containing protein, tyrosine phosphatase 2 (SHP2). Therefore, ITSM influences the functional transition from inhibition to activation [22–23].

Some activating receptor proteins do not have signaling motifs within their cytoplasmic domains. However, they facilitate signaling by forming complexes with ITAM-containing proteins. These include the ζ chain proteins, the T-cell receptor/CD3 complex, Igα and Igβ proteins associated with the B cell receptor, and the activating receptor of natural killer (NK) cells, NKG2D. The ITSM and ITIM contents vary among different ICCs. Inhibitory receptors (CD22 and FcγRIIB of B and NK cells) contain ITIMs within their cytoplasmic domains; e.g., T-cells PD-1 contains ITSMs and ITIMs. TCR signaling is characterized by receptor clustering induced by multivalent ligands, thereby activating the SRC family kinases. This conformational change promotes the SRC family kinase-catalyzed phosphorylation of the cytosolic ITAMs. These phosphorylated ITAMs are recognized by the tandem SH2 domains of the SYK or ZAP70 kinases. The recruitment of these kinases activates them, which then phosphorylate adapter proteins and enzymes that further actuate various signaling pathways [24–26].

In mature lymphocytes, intense signaling typically leads to clonal expansion, differentiation of naive lymphocytes into effector cells, and the acquisition of functions that facilitate an adaptive immune response. One way in which the TCR signaling intensity is altered is via the differential phosphorylation of ITAM tyrosines. The TCR complex comprises six signaling chains and 10 ITAMs. The more robust and prolonged the binding of an antigen to TCRs, the greater the ITAM phosphorylation. The levels of phosphorylated ITAMs provide a cytosolic interpretation of the strength of antigen–TCR binding and influence the nature of the cellular response. Activation followed by apoptosis may depend on the signaling intensity. Therefore, the magnitude of TCR signaling can be interpreted differently by lymphocytes, influencing their activation and transformation. Weak antigen receptor signaling is required for the survival of lymphocyte clones that express functional receptors; in contrast, strong signaling is needed to induce apoptosis in clones with self-reactive antigen receptors. However, clonal expansion, differentiation of naive lymphocytes into effector cells, and an adaptive immune response depend on signaling intensity. Changes in TCR signaling intensity are associated with the number of phosphorylated ITAM tyrosines. The more strong and prolonged the binding of an antigen to the TCR,

the more ITAMs are phosphorylated. Therefore, the affinity of antigens to TCRs and the nature of the immune response are related to the amount of phosphorylated ITAMs. The intensity of cell activation largely depends on the CD4, CD8, and CR2/CD21 coreceptors, which contain signaling-associated enzymes that phosphorylate ITAMs and stimulate the antigen receptors [27–28].

Signaling intensity is modulated by inhibitory receptors present on T-cells: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1, as well as CD22 and FcγRIIB of B-lymphocytes. Signals from these receptors and their costimulatory receptors determine the level of lymphocyte activation, a process that has been well studied. The costimulatory receptors do not bind with the antigens recognized by the corresponding receptor but with the ligands unique to antigen-presenting cells (APCs). Such costimulatory molecules include T-cell CD28, B7-1 (CD80), and B7-2 (CD86), which are expressed by the APCs. Though TCRs are morphologically similar to immunoglobulin receptors, important differences are evident (Fig. 3) [29–30].

Each TCR chain (α and β) consists of one Ig-like N-terminal V-domain, one Ig-like C-domain, a hydrophobic transmembrane region, and a short cytoplasmic region. The extracellular portion of the αβTCR is structurally similar to the antigen-binding fragment (Fab) of the Ig molecule, which comprises the V- and C-regions of the light and heavy chains. The V-regions of the α- and β-chains of TCRs contain short amino acid sequences where the most variable domains, i.e., complementarity-determining regions (CDRs), are concentrated. The three CDRs of each of the α- and β-chains together form a TCR domain that specifically recognizes the major histocompatibility complex (MHC) peptide (Fig. 4) [31].

Each TCR chain comprises segments encoded by several genes, which are connected during T-cell maturation. Proteins with ITAM motifs associated with TCRs may perform signaling functions. CD3 proteins and the ζ chain noncovalently bind to the αβTCR, forming a TCR complex. T-cells are activated when the TCR recognizes an antigen. The CD3 proteins and ζ chain are identical in all T-cell subsets, which is consistent with their role in signaling rather than antigen recognition [32–35].

Lymphocyte kinase (LCK) contains an SRC and noncovalently binds to the cytoplasmic domains of CD4 and CD8. The extracellular domains of these coreceptors bind to the MHC molecules present on the APCs, thus attracting these proteins to the TCR, which interact with the same MHC molecule. As a result, the LCK on the cytosolic surface of the plasma membrane contacts the ITAM within CD3 and the ζ chain. The LCK then phosphorylates the ITAM tyrosine residues, thus activating ZAP70. Therefore, the coreceptor provides the earliest enzymatic activity to initiate signals after the recognition of the peptide–MHC complexes by T-cells.

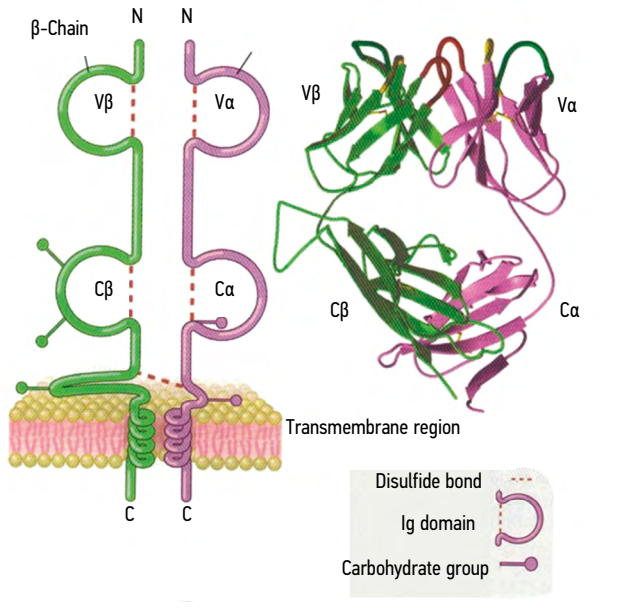

FIG. 3. T-cell receptor structure: N, C — terminal extracellular regions; Vβ, Vα — variable domains of α and β chains; Cβ, Cα — constant domains of α and β chains (adapted from [19] A.K. Abbas et al., 2022. Distributed under the terms of the CC-BY 4.0 license)

Рис. 3. Структура Т-клеточного рецептора: N, C — концевые внеклеточные области; Vβ, Vα — вариабельные домены α и β цепей; Cβ, Cα — константные домены α и β цепей (адаптировано из [19] A.K. Abbas и соавт., 2022. Распространяется на условиях лицензии CC-BY 4.0)

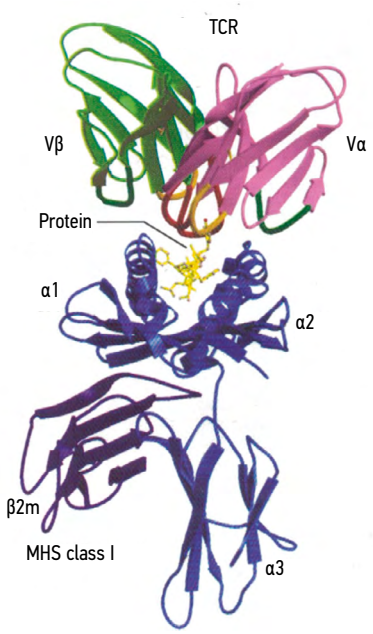

Fig. 4. T-cell receptor binding to the major histocompatibility complex: β2m — beta-2 microglobulin; α1–3 chains (adapted from [19] A.K. Abbas et al., 2022. Distributed under the terms of the CC-BY 4.0 license)

Рис. 4. Связывание Т-клеточного рецептора с главным комплексом гистосовместимости: β2m — бета-2 микроглобулин; α1–3 цепи (адаптировано из [19] A.K. Abbas и соавт., 2022. Распространяется на условиях лицензии CC-BY 4.0)

The central role during the TCR complex and coreceptor-based signaling is played by tyrosine and lipid kinases, which phosphorylate proteins and lipids, respectively [36–38].

The ζ-chain ITAMs are the docking sites for ZAP70, which contains two SH2 domains that bind to the ITAMs. The bound ZAP70 acts as a substrate for the proximal LCK, which phosphorylates specific ZAP70 tyrosine residues. As a result, ZAP70 also has a tyrosine kinase activity and can phosphorylate other cytoplasmic signaling molecules. The activation of signaling processes requires a critical threshold of ZAP70 activity that is achieved by the recruitment of several ZAP70 molecules to the phosphorylated ITAMs within the CD3 ζ-chains [39].

Another T-cell signaling pathway involves the activation of PI3 kinase, which phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) present on the inner leaflet of the plasma membrane to form PIP3. Therefore, proteins that contain PH domains bind to the interior parts of the cell membrane only when PIP3 is formed. Examples of such proteins include TEC tyrosine kinases such as the Inducible T-cell tyrosine kinase (ITK) of T-cells and the BTK of B cells; phospholipase Cγl (PLCγl); and key enzymes of the T-lymphocyte calcium signaling pathway. Activation of the alpha serine/threonine-protein kinase (AKT) promotes the phosphorylation of critical targets, protein synthesis, and metabolism, leading to cell proliferation and enhancing survivability. AKT activates a serine/threonine kinase called mechanistic target of rapamycin (mTOR), which regulates protein synthesis and cell growth by inactivating pro-apoptotic proteins and increasing the production and activation of the anti-apoptotic BCL-2 family proteins [40–41].

ZAP70-mediated tyrosine phosphorylation of the adapter proteins SLP76 and LAT is a key early step in T-cell activation. LAT directly binds with PLCγl and coordinates the recruitment of other adapter proteins, including SLP76, GADS, and GRB2, into a macromolecular complex, the TCR signalosome. Therefore, LAT is an activator of various components of the TCR signaling pathways. Antigen recognition (the physiological stimulus for ZAP70 activation) triggers signaling pathways leading to functional T-cell responses. Interaction between a T-cell and an APC forms an immune synapse or a supramolecular activation cluster (SMAC). The distance between the T-cell and the APC plasma membranes within the central region of the synapse (c-SMAC) is ~15 nm. Integrins remain at the synapse periphery, where they stabilize T-cell–APC binding, forming the peripheral portion of the SMAC (p-SMAC). In this external part of the synapse, the two membranes are ~40 nm apart. Thus, the synapse serves as the assembly site for the T-cell signaling apparatus, which includes the TCR complex, coreceptors, costimulatory receptors, and adapters. Although TCR-based signal transduction is initiated before synapse formation, the immune synapse itself provides a unique interface for TCR activation. T-cell activation is associated with the elimination of the drawback of low affinity of TCRs for peptide–MHC ligands and the presence of multiple MHC molecules presenting any one peptide on the APC. Therefore, the synapse is a site where repeated interactions of the TCR with a small number of peptide–MHC complexes on the APC occur, thus facilitating prolonged and efficient communication with T-cells. The c-SMAC is a crucial site for the exchange of signaling molecules. Subsequent degradation of signaling proteins contributes to the cessation of T-cell activation [20, 42–44].

G proteins involved in antigen recognition stimulate three Mitogen-activated Protein (MAP) kinases, which activate transcription factors and various cell types. RAS and RAC are two major members of this family that mediate the immune responses involving T-cells. RAS activates an extracellular receptor-activated kinase (ERK) and downstream transcription factors [45]. Once the cells are activated, the bound guanosine diphosphate (GDP) is replaced by guanosine triphosphate (GTP), inducing conformational changes in RAS proteins and activating enzymes. RAS activation is mediated by the TCR complex; the active RAS converts GTP to GDP and then returns to its normal, inactive state. Mutated RAS proteins can promote neoplastic transformation in many cell types. The mechanism of T-cell-based RAS activation involves the adapter proteins, LAT and GRB2. When LAT is phosphorylated, ZAP70 binds to GRB2, which then recruits the SOS exchange factor. This factor triggers the activation of rapidly accelerated fibrosarcoma, MAP kinase/ERK. ERK phosphorylates the E-26-like protein (ELK), which stimulates the transcription of the Activator Protein I (API). In parallel with SOS recruitment, adapter proteins activate GTP/GDP, which further actuate the RAC protein. RAC initiates the activation of the c-JUN N-terminal kinase (JNK; also known as stress-activated protein kinase [SAPK]). SAPK phosphorylates JUN, a component of the transcription factor, API. Besides ERK and JNK, MAP kinases contain p38, which also activates transcription factors. RAC induces cytoskeletal reorganization and may be involved in the clustering of TCR complexes, coreceptors, and other synaptic signaling molecules. ERC and JNC activities are blocked by tyrosine/threonine phosphatases, thus providing a negative feedback mechanism to terminate T-cell activation. TCR signaling activates the PLCγl, which further activates T-cell-specific transcription factors [19, 46–47].

After TCR activation, the adapter proteins LAT and SLP76 phosphorylate the tyrosine residues of ZAP70

to form a complex on the inner surface of the plasma membrane. PI3 kinase generates PIP3 and recruits the TEC family kinase, ITIC. These enzymes contain SH2 domains that bind to specific phosphorylated residues of LAT/SLP76. Here, ITIC phosphorylates and activates PLCγl, which then catalyzes the hydrolysis of PIP2 into the degradation products inositol 1,4,5-trisphosphate (IP3) and membrane-bound diacylglycerol (DAG). IP3 and DAG then activate the downstream T-cell signaling pathways. After the activation of T-lymphocytes, IP3 causes a rapid increase in the cytosolic free calcium levels and diffuses into the endoplasmic reticulum, releasing the stored calcium. Cytosol levels of calcium ions increase from resting (100 mmol/L) to peak (600–1000 mmol/L) levels within a few minutes. Depletion of the reticulum calcium is detected by the membrane protein stromal interaction molecule 1 (STIM1), which then activates the calcium release-activated channels (CRACs) [2, 8, 20].

CRAC activation increases cytosolic extracellular calcium levels to 300–400 mmol/L within 1 h. The ORAI protein is a key component of the CRAC channel. Mutations in *ORAI* can cause severe combined immunodeficiency. Cytosolic calcium binds to calmodulin to form complexes that activate enzymes, such as calcineurin and protein serine/threonine phosphatase, which are vital for the activation of the DAG transcription factors. PIP2 is a membrane-bound lipid that activates protein kinase C (PKC). Multiple PKC isoforms are involved in the generation of active transcription factors. Increased cytosolic free calcium levels and DAG induce conformational changes in the PKC isoforms. The PKCθ isoform is involved in the transcriptional activation of the nuclear factor kB (NF-kB) [48–49].

Consisting of the FOS and JUN protein dimers, the API of T-cells is activated by TCR-mediated signals. This process involves the synthesis of the FOS protein and phosphorylation of the preexisting JUN protein, catalyzed by MAP kinases. In the nucleus, API binds to the Nuclear Factor of Activated T-cells (NFAT) transcription factor. API activation represents a convergence point for several TCR-initiated signaling pathways [12, 16, 20, 50–52].

NF-kB is also activated by TCR signals. NF-kB proteins are homologous to c-RELs and are vital for the transcription of many genes in various cell types. The NF-kB pathway is involved in lymphocyte activation as well as the Toll-like receptor (TLR)- and cytokine receptor-based signaling responses. Establishing the relationships between different signaling proteins, the activation of transcription factors, and the functional responses of T-cells is challenging because the interactions between signaling pathways are complex and have not been fully understood [1, 19, 44].

An additional mechanism for regulating T-cell activation involves microribonucleic acids (miRNAs), which mediate the post-transcriptional inhibition of gene expression. miRNAs are transcribed from the nuclear DNA as long primary transcripts, which are processed by the Drosha endoribonuclease into shorter pre-miRNAs. These are exported to the cytosol, where they are further processed by another endoribonuclease, Dicer, into short, double-stranded miRNAs, 21–22 bp each, which bind to the Argonaute proteins to form the RNA-induced silencing complexes . One strand of miRNA binds to a complementary mRNA; perfect complementarity targets the mRNA for degradation. However, if imperfect, mRNA translation is partially inhibited, suppressing the levels of the corresponding proteins. In T-cells, miRNA expression is reduced after activation with the degraded Argonaute protein, which increases the contents of proteins required for cell cycle progression [37, 39, 43, 53, 54].

Therefore, multiple signaling pathways are initiated by ligand binding to the TCR, which activate different types of enzymes. They include the G protein and MAP kinase pathways that activate the ERK and JNK kinases, the PLCγ1 calcium-dependent pathway that activates calcineurin, and the DAG-dependent pathway that activates the PKC. Each of these pathways contributes to the expression of genes encoding proteins required for the clonal expansion, differentiation, and effector functions of T-cells. Enzymes induced by TCR signaling activate transcription factors that bind to the regulatory regions of T-cell genes and enhance their transcription. The main source of information on the transcriptional regulation of T-cell genes is the analyses of cytokine gene expression, the transcriptional regulation of most T-cell cytokine genes, and transcription factors required for the maximal expression of Interleukin-2 *(IL-2)* [1, 2, 5]. Transcription factors are activated by different cytoplasmic signaling pathways; therefore, the activation of multiple transcription factors explains the need for numerous signaling pathways after antigen recognition. The three transcription factors in T-cells, NFAT, API, and NF-kB, which are activated after antigen recognition, are most likely critical for the T-cell-mediated immune response. NFAT is required for the expression of genes encoding IL-2, Interleukin-4, and tumor necrosis factor (TNF). Calcineurin dephosphorylates NFAT, thus allowing it to translocate to the nucleus, where it binds to the regulatory regions of *IL-2* and API [50–51].

Modulation by protein tyrosine phosphatases that inhibit TCR signaling is another mechanism for T-cell signaling. SHP1 and SHP2 inhibit key signaling molecules and thus functionally neutralize tyrosine kinases. Similar to SHP1 and SHP2, SH2-domain-containing Inositol Phosphatase (SHIP),

another inhibitory phosphatase, binds to ITIMs through specific inhibitory receptors. By dephosphorylating PIP3, SHIP inhibits PI3-kinase-based signaling [2, 6, 16, 45].

The receptor tyrosine phosphatase, CD45, is a key participant in signaling involving the receptors of most cell types. CD45 imbalance underlies many immunodeficiency, autoimmune, and cancer diseases. CD45 dephosphorylates the inhibitory tyrosine residues in SRC family kinases (including LCK and proto-oncogene tyrosine-protein kinase [FYN] in the T-cells), thus promoting the activation of these kinases. The costimulatory receptors CD2/SLAM contribute to T-cell activation and differentiation. Human T-lymphocyte CD2 functions as an intercellular adhesion molecule and a signal transducer. SLAMs are a separate subgroup within the CD2 family of proteins. SLAMs contain two extracellular Ig domains and a long cytoplasmic region with an ITSM that differs from the ITAMs and ITIMs found in other activating or suppressing receptors. The T-cell and DC SLAMs can interact, thus facilitating signal transmission to T-cells. Binding to the signaling lymphocytic activation molecule-associated protein (SAP), the ITSM forms an SLAM–SRC family kinase bridge, which is associated with the T-cell CD3 protein, FYN. SLAM and other members of its family function as costimulatory receptors for NK and certain B cells. 2B4 is another important member of the SLAM family; it binds to the SAP adapter protein, induces activation signaling, and recruits FYN. Defective 2B4-based signaling contributes to the development of X-linked lymphoproliferative syndrome (XLP) because 2B4 suppresses NK cell-mediated cytolysis. The activation of T-lymphocytes is associated with metabolic changes, ensuring a cell-mediated immune response. Glucose transport increases, and mitochondrial oxidative phosphorylation (glycolysis)-based energy production changes even under large amounts of oxygen (aerobic glycolysis or the Warburg effect). Aerobic glycolysis in lymphocytes may be important for cell proliferation, the differentiation of T-cells into effector cells, and the secretion of proinflammatory cytokines [9, 13, 21, 29, 35, 49, 55].

CONCLUSION

Initiation of cell surface receptor-based signaling requires the ligand-induced clustering of receptor proteins (cross-linking). It also involves a conformational change within the receptor induced by its association with the ligand. Cell surface signaling receptors initiate cytosolic signaling, followed by a nuclear phase during which gene expression patterns change. Different types of signaling receptors contribute to the activation of innate and adaptive immune responses. The most important category is NRTKs that phosphorylate the ITAMs within the cytoplasmic domains of receptor complex proteins. Tyrosine kinases, nuclear receptors, heterotrimeric serpentine receptors coupled to the G protein, and Notch family receptors are involved in the activation of T-cells and the induction of adaptive immune responses. The intensity of the immune response depends on the affinity and valence of the antigen that recruits different amounts of ITAMs. CD4 and CD8 T-cell coreceptors enhance signaling that involves antigen receptors. This process can be attenuated by the inhibitory CD22 and PD-1 receptors, which contain the cytosolic immunoreceptor inhibitory ITIMs and ITSMs. TCR ligation results in the phosphorylation of tyrosine residues in CD3 and ζ ITAM, catalyzed by the SRC family of kinases and the recruitment of ZAP70. In this case, each SH2 domain of ZAP70 binds to one phosphorylated tyrosine of the ITAM. The activated ZAP70 kinase phosphorylates the tyrosine residues of the adapter proteins, and the resulting enzymes are recruited to signalosomes.

Enzymes that mediate GDP/GTP exchange in G proteins, such as RAS and RAC, activate the MAP pathway. These further actuate JUN and FOS, which are components of the API. The activation of PLCγl promotes the release of IP3 from PIP2; IP3 induces calcium release from intracellular stores. Calcium depletion triggers the opening of the CRAC, which is activated by calcium release. Calcium binds to calmodulin and activates calcineurin, a phosphatase that promotes NFAT entry into the nucleus.

DAG is formed within the membrane when PLCγl releases IP3 from PIP2. DAG can activate PKCθ, which can promote NF-kB activation. The PI3 lipid kinase converts PIP2 to PIP3. PIP3 recruits proteins that contain a PH domain to the plasma membrane and also activates them. PIP3 actuates T-cell ITK, activating the PDK1 kinase, which in turn phosphorylates the AKT kinase; this kinase is involved in cell survival.

Attenuation of the T-cell immune receptor signaling is mediated by receptors that contain inhibitory tyrosine-containing motifs within their cytoplasmic regions and recruit phosphatases. Another critical signal attenuation mechanism involves the ubiquitination of signaling proteins by E3 ubiquitin ligases, which label them for degradation.

The cytokine receptors that participate in signaling by employing the non-receptor-based janus kinases (JAK) tyrosine kinases to phosphorylate the signal transducers and activators of transcription factors are not discussed in this article. Post phosphorylation, they are translocated to the nucleus where they induce the transcription of target genes. The receptors for many proinflammatory cytokines (Interleukin-1, Interleukin-17, TNF, etc.) activate either canonical or non-canonical NF-kB signaling. The former

involves TLRs, cytokine receptors of the TNF family. This pathway comprises the activation of the IKKβ kinases, phosphorylation of the Inhibitor of IkBα by the activated IKKβ, ubiquitination and proteasomal degradation of IkBα, and the transport of NF-kB into the nucleus.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

The contribution of each author. A.V. Moskalev, development of a general concept, writing an article, data analysis; B.Yu. Gumilevskiy, development of a general concept, research design; V.Ya. Apchel, research design, editing, data analysis; V.N. Tsygan, development of a general concept.

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