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The role of actomyosin and the microtubular network in both the immunological synapse and T cell activation

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TABLE OF CONTENTS

1. ABSTRACT

The formation of immunological synapses between T cells and APCs, as well as the functions associated with this structure, like cytokine secretion and the lysis of infected cells, are critical processes in the immune response. The T cell cytoskeleton is involved in these activities and this has been the subject of numerous studies in recent years. Although the importance of the T cell actin network is evident, the participation of microtubules and myosin motors in the formation of immunological synapses and T cell effector functions has also been assessed. This review provides an update on the role of cytoskeletal networks and related molecules in the activation of T lymphocytes.

2. INTRODUCTION

Leukocytes play a key role in inflammation as well as in both innate and adaptive immunity. These activities require a highly regulated cytoskeleton, that permits the leukocyte membrane to reorganize, facilitating receptor re-localization, the recruitment of signaling molecules and changes in cell morphology (1). Accordingly, when T lymphocytes are stimulated by signals from the environment, a complex repertoire of responses leading to their activation can be observed, including the development of cell polarity and the remodelling of the actin cytoskeleton (2). Optimal T cell activation relies on the T cell receptor (TCR) binding to its specific antigenic peptide that is bound to major

histocompatibility (MHC) molecules on the surface of antigen presenting cells (APCs), as well as on different co-stimulatory signals (3).

The role of the lymphocyte cytoskeleton in cell motility and effector functions has been thoroughly studied. It is very likely that the T cell cytoskeleton determines the efficiency and fidelity of the immune response (4), promoting the amplification of the TCR signals and the effector functions of the activated T cells. The clustering of actin filaments must be considered among the cytoskeletal rearrangements that occur in T cells during their activation (5). Similarly, the reorientation of the microtubule organizing center (MTOC), along with the secretory apparatus associated at the contact site with an APC must also be taken into account (6). The remodelling of the actin cytoskeleton in T cells permits an intimate contact to be established with the APC, facilitating the sustained signaling required for cell activation. The reorientation of the MTOC augments the efficiency of the lytic event (for CD8+ cells), or the release of cytokines (for CD4+ cells) toward the APC (2). The possible role of myosin in these processes has also been addressed (7-9).

The rearrangements in the T cell cytoskeleton are coupled with a relocalization and segregation of surface receptors, adaptor proteins and signaling molecules at the immunological synapse (IS). In addition, it has been demonstrated that the integrity of the cytoskeleton of dendritic cells (DCs, a specific type of APC) is required for the accumulation of filamentous actin at the IS in T cells (10). This review provides an update of the role of the T cell cytoskeleton in IS formation, focusing on actomyosin and microtubule networks, the activation of T lymphocytes and their effector functions.

3. THE IMMUNOLOGICAL SYNAPSE AND THE CYTOSKELETON OF T LYMPHOCYTES

Activation of T lymphocytes during the formation of the IS requires the interaction of the TCRs with antigenic peptides bound to MHC molecules on the membrane of the APCs. The IS contains two major functional domains: the central supramolecular activation complex (cSMAC) and the peripheral SMAC (pSMAC). The cSMAC contains the TCR-CD3-peptide-MHC complexes, costimulatory molecules (CD28 and CD2) and several associated signaling molecules (Lck, Fyn and PKC theta). In contrast, the pSMAC includes some adhesion and cytoskeletal molecules such as LFA-1 and talin (11-14). The IS is implicated in the directed secretion of cytokines and the integration of positive and negative signals that determine the extent of the immune response (15). It has been proposed that the TCRs clustered at the IS are endocytosed, thus allowing TCR signaling to decline (16).

Upon encountering an APC bearing a specific antigen, the T cell undergoes dramatic cytoskeletal rearrangements that impair migration, causing the uropod to retract and the leading edge to flatten against the APC surface. Moreover, the T cell MTOC re-orientates towards the site of contact with the APC (4). The localization and clustering of receptors, signaling molecules and cytoskeletal components at the T cell-APC interface is essential for efficient T cell activation. However, while the T cell cytoskeleton seems to be crucial for this activation, many important questions remain unanswered. Actin and actin-binding proteins transiently accumulate at the T cell-APC interface, a process that is dependent on the engagement of both TCR and costimulatory receptors, like CD28. In this regard, sustained actin dynamics is required for the accumulation of TCR/MHC in the cSMAC, and for the efficient induction of T cell proliferation. Furthermore, the control of specific actin dynamics by the TCR and costimulatory molecules is a mechanism that regulates the predisposition to T cell activation (17). Accordingly, it has been shown that latex beads coated with anti-TCR antibodies are sufficient to induce F-actin polymerization at the cell-bead contact site (18, 19).

3.1. The actomyosin cytoskeleton and the immunological synapse

The actomyosin network of the T cell plays a key role in the formation of the IS. Indeed, exposure to the inhibitor of actin polymerization cytochalasin D is sufficient to prevent IS formation (20). Aside from its critical role in the formation of the IS, the actin cytoskeleton also seems to be involved in T cell activation at other levels. This not only includes the changes in cell shape induced by the cytoskeleton, but also the fact that it acts as a scaffold for signaling molecules and in the segregation of signaling elements like Lck, Fyn and PKC theta within the SMACs, a critical step for full T cell activation (14). Accordingly, it has been shown that talin, vinculin, paxillin, fimbrin, Pyk2 and other cytoskeleton-organizing molecules are phosphorylated and subsequently activated after TCR engagement (21) (Figure 1). In addition, the ERM (ezrin-radixin-moesin) proteins, which act as linkers between the plasma membrane and actin cytoskeleton, participate in the formation of the SMACs (22-25) (Figure 1). ERM proteins are rapidly inactivated in T cells after antigen recognition through a Vav1-Rac1 pathway. This inactivation results in the disassociation of the cortical actin cytoskeleton from the plasma membrane, producing a decrease in the cellular rigidity and allowing a more efficient T cell-APC contact.

The actin-binding protein HIP-55 (a substrate of Src/Syk kinases) (Figure 1) can be found at the T cell-APC contact site in an antigen-dependent manner, and its recruitment seems to regulate TCR signaling and endocytosis (26). However, HIP-55 does not seem to participate in IS formation but it is more likely that it regulates T cell activation in subsequent processes, linking TCR and the actin cytoskeleton to gene activation and endocytosis. Another recently identified actin-related cytoskeletal protein that is a target of TCR signaling is α-adducin, a protein that caps the fast-growing end of actin filaments and recruits the cytoskeletal protein spectrin to actin. Furthermore, alpha-adducin associates with Fyn and calmodulin, it is a substrate for PKC and it is modified and down-regulated upon TCR engagement. Therefore, this protein might act as a mechanical link between receptor-

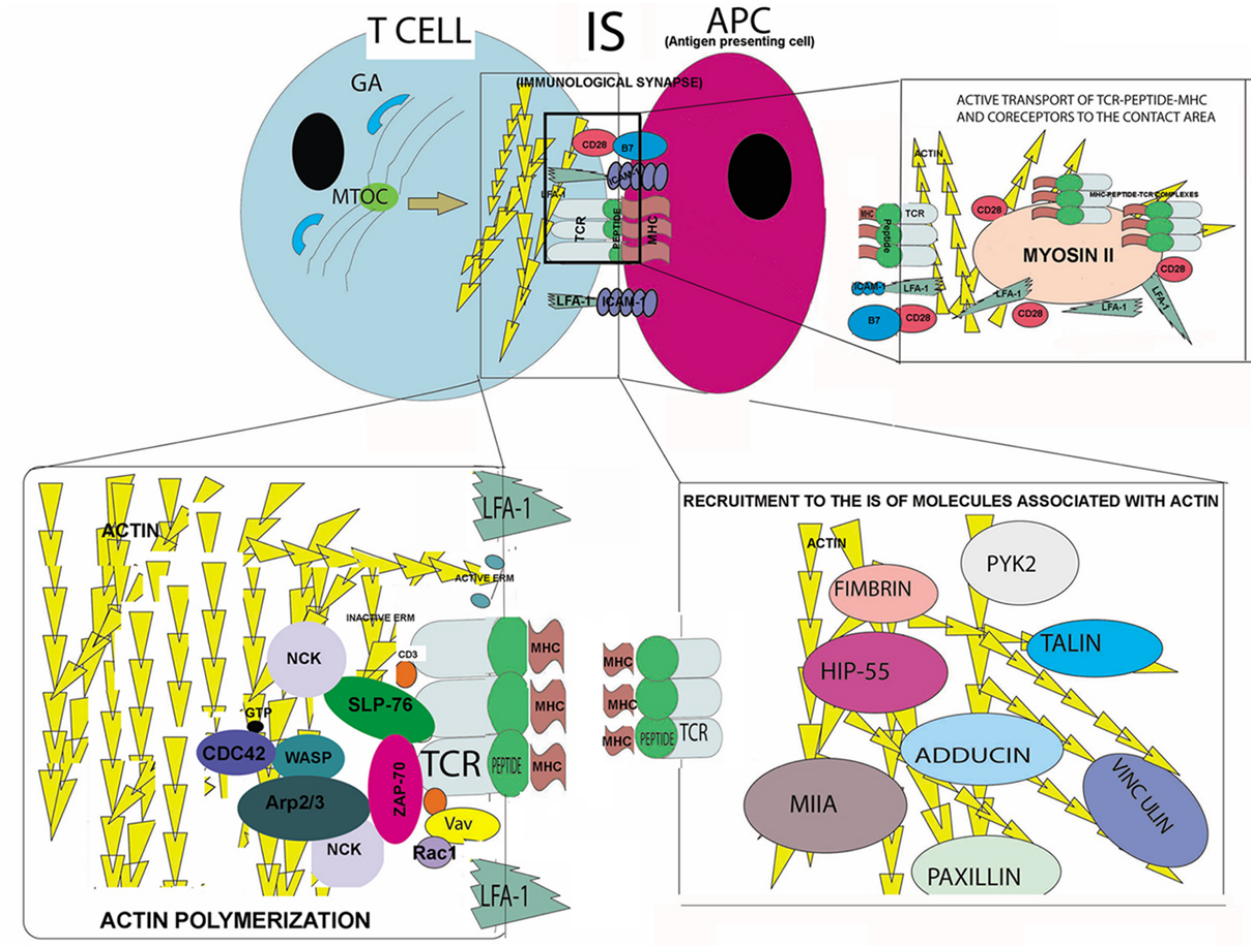

Figure 1. Role of the actomyosin cytoskeleton in T cell activation and the formation of the immunological synapse (IS). The boxed area at the bottom left of the figure depicts the recruitment of different signalling molecules to the contact zone between the T cell and APC, which ultimately leads to actin polymerization during T cell activation. Upon TCR engagement by specific antigenic peptides, the TCR-associated zeta chain and CD3 molecules in T cells are phosphorylated by Src kinases, such as Lck. This allows ZAP-70 to be recruited, which in turn phosphorylates LAT providing an anchor for SLP-76. LAT can also recruit Vav and Nck to the nascent synapse and Nck in turn recruits WASP, which binds directly to a powerful actin nucleator, the Arp2/3 complex. Vav activates the GTPases Cdc42 and Rac. The box at the bottom right shows a range of molecules implicated in actin dynamics that are recruited to the immunological synapse during T cell activation. Among them are cytoskeletal proteins like vinculin, talin, fimbrin, alpha-adducin and HIP-55, kinases like Pyk2 and the actin-based molecular motor MIIA. The boxed area at the upper right part of this figure represents the mechanism by which CD28 and LFA-1, essential for T cell activation, are transported to the T cell-APC interface. The cortical actin cytoskeleton and its associated molecules are transported by myosin II to the contact area, increasing the amplitude and duration of T cell signalling.

mediated signaling and the regulation of the actin network in the T cell (27) (Figure 1).

As stated above, the activation of T cells requires the engagement of co-stimulatory receptors and adhesion molecules, mainly CD28 and LFA-1 that interact with B7.1/B7.2 (CD80/CD86) and ICAM-1, -3, respectively. The engagement of costimulatory molecules triggers the accumulation of signaling molecules at the T cell interface, and this is driven by the movement of the cortical actin cytoskeleton and the molecules attached to it. This movement seems to be an active process as it is dependent on myosin II (9) (Figure 1). Moreover, it serves to increase the overall amplitude and duration of T cell signaling.

Upon TCR engagement, a rapid increase in the association of filamentous actin and an activation-dependent association of filamentous actin with the TCR zeta chain occurs (14, 28). However, approximately 30-40% of TCR zeta molecules at the surface of resting T cells are linked to the actin cytoskeleton. This phenomenon is not entirely understood, but it could reflect a negative regulatory influence on signal transduction through the sequestration of kinases such as Lck, thereby preventing their phosphorylation (29-31). The cytoplasmic domains of CD3 and the zeta chain associated with the TCR contain immune-receptor tyrosine based activation motifs (ITAMS), which are phosphorylated by Src kinases (mainly Lck) following TCR engagement. These ITAMS are

necessary for TCR-induced actin polymerization (32). The phosphorylation of the TCR ITAMs facilitates the recruitment of ZAP-70, which Tyrosine phosphorylates LAT and serves as an anchor for SLP-76 (14). The involvement of the actin cytoskeleton in this activation process is not obvious, but phosphorylation events may play an important role in nucleating the actin cytoskeleton around LAT, possibly by recruiting Vav and Nck that both associate with the cytoskeleton (33). In turn, Nck recruits WASp, a protein restricted to haematopoietic cells that binds directly to the Arp2/3 complex, a crucial regulator of actin polymerization. Nck also binds directly to the CD3-epsilon tail in an ITAM-independent manner, and it is rapidly recruited to the IS (34). In addition, Vav activates members of the Rho family of GTPases, like Cdc42 and Rac. While activated Cdc42 forms thin actin projections called filopodia, Rac generates lamellipodia, that are areas of very active actin polymerization forming "ruffles" at the outer edge of the IS. Active Cdc42 also activates a complex that includes N-WASP and WIP (35).

The recruitment of the key proteins listed above to the IS induces the dramatic polymerization of actin that occurs during T cell activation. Accordingly, mice deficient in Vav1 or WASp show defects in T cell activation and actin polymerization (36, 37). As expected, patients with WASp deficiency (suffering from Wiskott-Aldrich syndrome) also display defects in T cell activation and actin-based structures (38), leading to immunodeficiency. It has recently been found that the Tec kinase, Itk, is a key element in the localized polymerization of actin at the IS, through the activation of Cdc42 and WASP. Accordingly, *Itk*$^{-}$*/Itk*$^{-}$ mice cells suffer defects in actin polymerization and T cell-APC conjugate formation. The impaired recruitment of Cdc42 also observed in these cells suggests that Itk is also involved in the relocalization of Vav to the IS (39).

A functional link between costimulatory receptors like CD28 and several signaling molecules that interact with the actin cytoskeleton during T cell activation has also been described. CD28 enhances Vav1 activation, which contributes to the activation of NF-AT through the TCR. In fact, upon Vav overexpression, ligation of CD28 seems to be sufficient to activate NF-AT in the absence of TCR engagement. Thus, CD28 engagement would potentiate TCR signaling via a synergistic collaboration between Vav1 and SLP-76, and probably through changes in cortical actin (40). CD28 engagement also promotes actin polymerization through the activation of Cdc42 (41), which induces the formation of filopodia.

For IS formation, it is important that the migrating T cell receives a stop signal, defined by the cooperation between adhesion molecules, the actin cytoskeleton and the TCR (42). A role has recently been identified for the non-muscle myosin IIA motor protein in generating this stop signal. However, this protein does not seem to be involved in the formation of the IS (8). When the T lymphocyte stops migrating and binds to the APC, integrins and the majority of the engaged TCRs cluster in the T cell. After a few minutes, the engaged TCRs are relocated to the center of the cell-cell contact area (cSMAC), whereas the engaged integrins concentrate in a peripheral ring (pSMAC). Interestingly, the TCR initially displays a bipolar distribution, with small clusters in the zone of the nascent synapse and a large cluster at the opposite side of the cell. A few minutes later, the small TCR clusters coalesce at the cSMAC, and the TCR clusters located at the distal pole of the cell relocates to this central area. This apparently bizarre behaviour of the TCR is probably due to the activation of myosin II and the contraction of the actin filaments of the cell uropod (9, 14). This hypothesis was reinforced by the observation that their orthologues in the amoeba *Dictyostelium discoideum* are required for receptor capping (43). However, there is no evidence that T cell myosins fulfil a functional role during TCR-mediated cytokine secretion.

Active movement of the cortical actin cytoskeleton, also through myosin motors, would move molecules linked to this cytoskeleton towards the T cell-APC interface. In this model, stabilization of the actin filaments would be necessary and the activity of cofilin, a protein that dissassembles actin filaments, would potentially be important. By inhibiting cofilin (through the PAK or LIM kinases) the half-life of actin filaments may be extended, and these could then be contracted for longer periods of time by activated myosin II (44). Interestingly, myosin V has been seen to colocalize with MHC class II molecules in mononuclear blood cells, and this myosin is up-regulated by T-lymphocyte activation (7). Nevertheless, the possible functional consequences of this association remain to be determined. The importance of myosin motors in processes related to T cell activation is further highlighted by the phosphorylation and subsequent activation of the myosin light chain after TCR engagement (21). However, the precise role of myosins in T cell activation also needs to be further explored.

During the formation of the IS, it is likely that sites of integrin engagement are generated by actin polymerization, nucleated at the membrane by the Arp2/3 complex. The zones of the T cell surface rich in active actin protrusions seem to be more sensitive to stimulation by MHC-peptide complexes on the APC (45). In addition, the function of LFA-1 in these cellular protrusions is also regulated by the actin cytoskeleton. Thus, TCR engagement seems to disassemble the cortical actin cytoskeleton, through the action of calpain and other proteases. This phenomenon releases LFA-1 from its anchorage to actin, allowing it to move from the cSMAC towards the pSMAC (14, 46). By using these adhesion mechanisms, the barrier effect of the negatively charged glycocalyx of the T cell and the APC can be overcome (14). Actin polymerization at the IS therefore stabilizes and favours the sustained signaling induced through the TCR (47).

Soon after the initial TCR-triggered signal, different tyrosine kinase families are activated, such as the Src, Syk and Tec families (reviewed in (48)). These kinases activate pathways that feedback to maintain a functional synapse. This feedback promotes the reorganization of the actin cytoskeleton and favours cell adhesion by activating the adhesion and degranulation protein (ADAP) that links

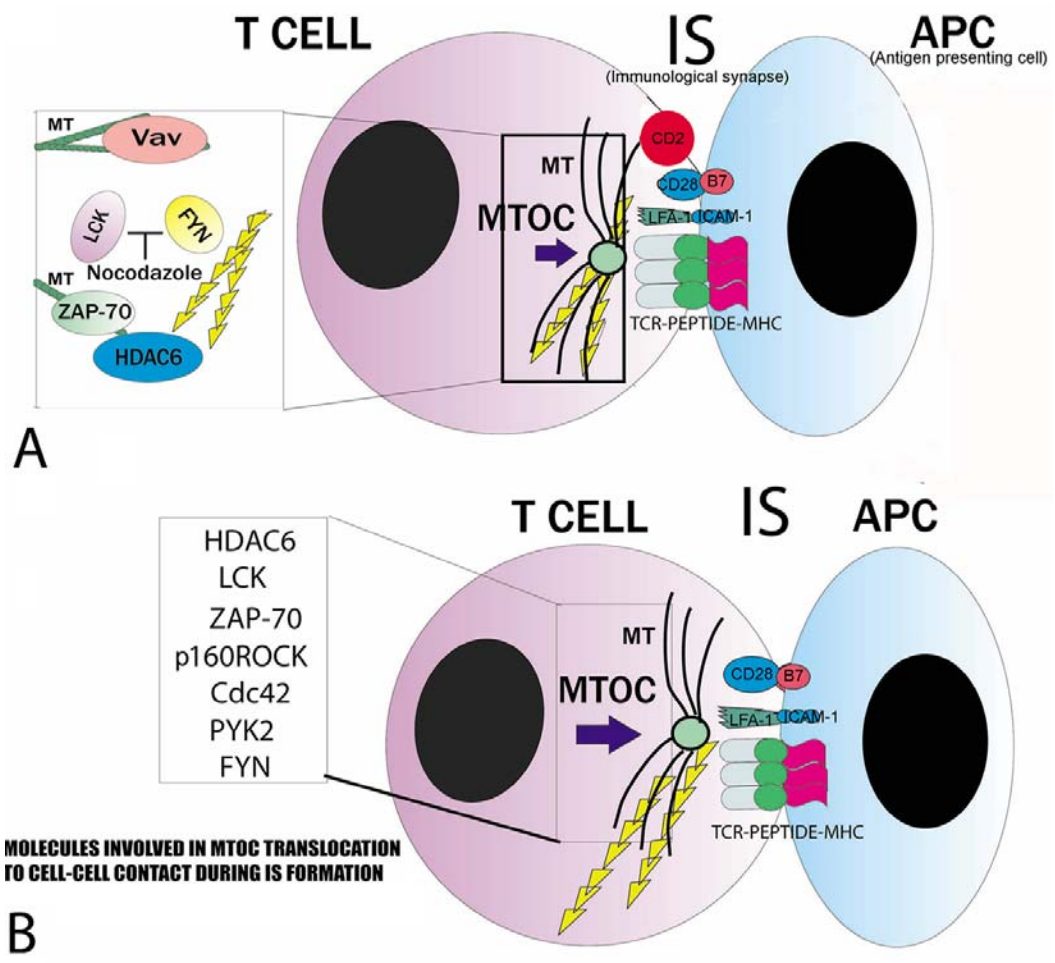

Figure 2. Role of the microtubular network in T cell activation and immunological synapse (IS) formation. A. The box at the upper left of the figure shows several molecules interconnected with the microtubular network that have been implicated in the formation of the immunological synapse and T cell activation. Vav and ZAP-70 are two molecules implicated both in the dynamics of the actin and tubulin cytoskeleton. HDAC6 is a tubulin deacetylase that is also implicated in MTOC translocation during IS formation. Hence, the inhibitory effect of microtubule-disrupting drugs like nocodazole in Lck and Fyn is indicated. B. A key feature of IS formation is the translocation of the microtubule organizing center (MTOC) to the contact zone between the T cell and the APC. The box on the left shows the different signalling molecules so far implicated in this phenomenon, including protein-kinases like Lck, p160ROCK, Fyn, ZAP-70 and Pyk2, GTPases like Cdc42 and the tubulin deacetylase HDAC6.

LFA-1 function to the TCR signals (49, 50), also known as the Fyn binding protein (FYB), SLAP-130/Fyb or Fyb/SLAP. The mechanism by which ADAP couples TCR stimulation to the regulation of integrin avidity is unclear, but there is evidence that this protein is required for the clustering of the LFA-1 integrin (46). The proline-rich tyrosine kinase 2 (Pyk2) is in turn rapidly translocated to the vicinity of the immune synapse after TCR triggering, and this requires both functional Lck and the presence of phosphorylated ITAMs. However, the precise role of Pyk2 in T cell activation is still not clear (51).

3.2. The tubulin cytoskeleton and the immunological synapse

The involvement of tubulin networks in T cell activation and IS formation has been addressed in several studies. One of the most important phenomena during the formation of the IS is the reorientation of the MTOC and the secretory machinery of the T cell towards the contact area with the APC. This process directs the delivery of cytokines to the appropriate cells (52). MTOC repositioning is a complex event that is dependent on TCR signaling. It involves the shortening of microtubules and the subsequent anchoring of the MTOC at the site of TCR engagement (53). Neither strong actin structures nor talin accumulation are required at the zone of the membrane towards which the MTOC reorientates (18) (Figure 2).

Different kinases, such as Lck and ZAP-70, regulate MTOC reorientation through the phosphorylation of alpha-tubulin, a key element in the regulation of microtubule polymerization. Accordingly, MTOC translocation is inhibited in T cells that are deficient in Lck (32), or ZAP-70 (54), albeit to a different extent. However,

ZAP-70 does not seem to be involved in the redistribution of T cell surface receptors at the IS (54). The potential role of kinases located at the MTOC in regulating its reorientation has also been addressed. Accordingly, Pyk2 interacts with different signaling proteins that seem to mediate MTOC translocation (55). In this regard, Pyk2 collaborates with Fyn to inactivate the Rho GTPase-activating protein PSGAP, in turn activating Cdc42, an important mediator of MTOC translocation (56). Interestingly, Fyn localizes to the MTOC (57) and regulates MTOC relocation at the IS (Sancho *et al.*, unpublished data). As well as regulating actin polymerization, Cdc42 also seems to be implicated in controlling the positioning of the MTOC. Hence, dominant negative and constitutively active forms of Cdc42 block MTOC reorientation in T cells (58). The GTPase RhoA also seems to be implicated in MTOC reorientation, and its effector molecule p160ROCK associates with the centrosome and regulates its position (59) (Figure 2).

Interactions between important molecules in the TCR signaling pathway, like Fyn (60), ZAP-70 and Vav (61), and tubulin have been also reported. Hence, microtubules appear to influence these signaling pathways, perhaps by controlling their intracellular distribution. A recent study has also shown that the level of tubulin acetylation, regulated by the tubulin deacetylase HDAC6, plays an important role in the organization of the IS and the synthesis of IL-2 by T cells. The tubulin deacetylase HDAC6 has also been implicated in the reorientation of the MTOC at the IS (62). Moreover, HDAC6 associates with motor proteins of the dynein family and this probably contributes to the transport of the MTOC towards the IS (63).

Other signalling molecules that seem to be involved in the repositioning of the MTOC are the microtubule associated proteins (MAPs) and the microtubule-destabilizing factors. Since MAPs stabilize microtubules, it is feasible that microtubule-destabilizing factors are activated during T cell activation, thereby inhibiting MAPs and increasing microtubule depolymerization (57).

4. EFFECTOR FUNCTIONS

4.1. Cytotoxicity, granule secretion and the cytoskeleton

Cytokine secretion requires the formation of a functional IS. After the initial T cell-APC interaction, the T-cell MTOC moves to the cell-cell contact region, generating microtubules that support the traffic of vesicles. Polarized secretion of cytokines occurs across the IS and contributes to the activation of the APC (Figure 2).

TCR-mediated signals require the coordinated activation of ZAP-70 and its adaptor LAT and SLP-76, to induce the sustained mobilization of calcium necessary for MTOC relocation to the IS (64). TCR-mediated granule exocytosis of perforins and granzymes, which mediate the cytotoxic activity of cytotoxic T lymphocytes (CTL), is mediated by calcium influx and PKC activation (64-68). It was initially thought that calcineurin and CaMK might mediate the TCR-induced intracellular flux of calcium, however, these molecules do not appear to be involved in this phenomena (64). It is more likely that myosin motors or other actin-associated molecules are responsible for this calcium-dependent MTOC relocation. In this regard, Cdc42 drives both the actin polymerization and MTOC translocation produced via the TCR. However, the actin remodelling mediated by Cdc42 is not involved in the synthesis of IL-2 by T cells (55). Accordingly, the reorientation of the MTOC and the lytic granules toward the IS is inhibited when ERK activation is blocked (69, 70) (Figure 3). In addition, the weak cytolytic activity of some tumour-infiltrating lymphocytes is due to defective MTOC translocation that precludes lytic granule exocytosis, rather than to impaired TCR-mediated signalling (71). Nevertheless, there is evidence indicating that lytic granule exocytosis may occur independently of MTOC translocation (69). Therefore, it is likely that the reorganization of the actin and tubulin cytoskeletons is co-ordinated, and that their associated adaptors regulate TCR-signaling by generating a very complex network sensitive to antigen recognition processes.

The involvement of the actin cytoskeleton in secretion is very evident in patients suffering from the Wiskott-Aldrich syndrome (WAS). This is a X-linked immunodeficiency associated with altered T cell morphology, defective TCR-induced actin polymerization and proliferative responses (reviewed in (72)) (Figure 3). Accordingly, INF gamma secretion and polarization of this cytokine towards an antigen-bearing target is severely impaired in CD4+ T cells deficient in WASp (73).

T cell anergy is an active process in which cells stimulated in the absence of efficient co-stimulation become non-responsive to the subsequent exposure to their cognate antigen. This phenomenon serves as a way to control the responses to self-antigens in the periphery. T cell anergy is associated with calcium mobilization and defective IL-2 production, leading to a block in cell division and proliferation (reviewed in (74)). Recently, high levels of expression of the ADP-ribosylation factor-6 (ARF6), a member of the ARF family of GTPases involved in membrane trafficking and regulation of the cortical actin cytoskeleton, has been correlated with T cell anergy. Indeed ARF6 has been proposed as a marker for anergic T cells *in vivo* (75). *In vitro* studies demonstrate that forced expression of ARF-6 in T cells prevents TCR-mediated reorganization of cortical actin, ERK activation, and IL-2 transcription and secretion (75). The mechanism by which ARF-6 alters TCR-mediated T cell activation and cytokine secretion is still unclear, but ARF-6 may affect positive TCR-dependent activation by disturbing the reorganization of the actin cytoskeleton, inhibiting Rho GTPases, and altering TCR endocytosis and trafficking to the cell surface (reviewed in (76) (Figure 3).

Cytotoxic T Lymphocytes (CTLs) or Natural Killer (NK) cells form fully functional IS's with target cells (77, 78). In these short-lived synapses, a secretory domain is formed between the cSMAC and pSMAC that directs the secretion of lytic granules, and that is localised around the MTOC (1, 79). In CTL, cytoskeletal polarization of both

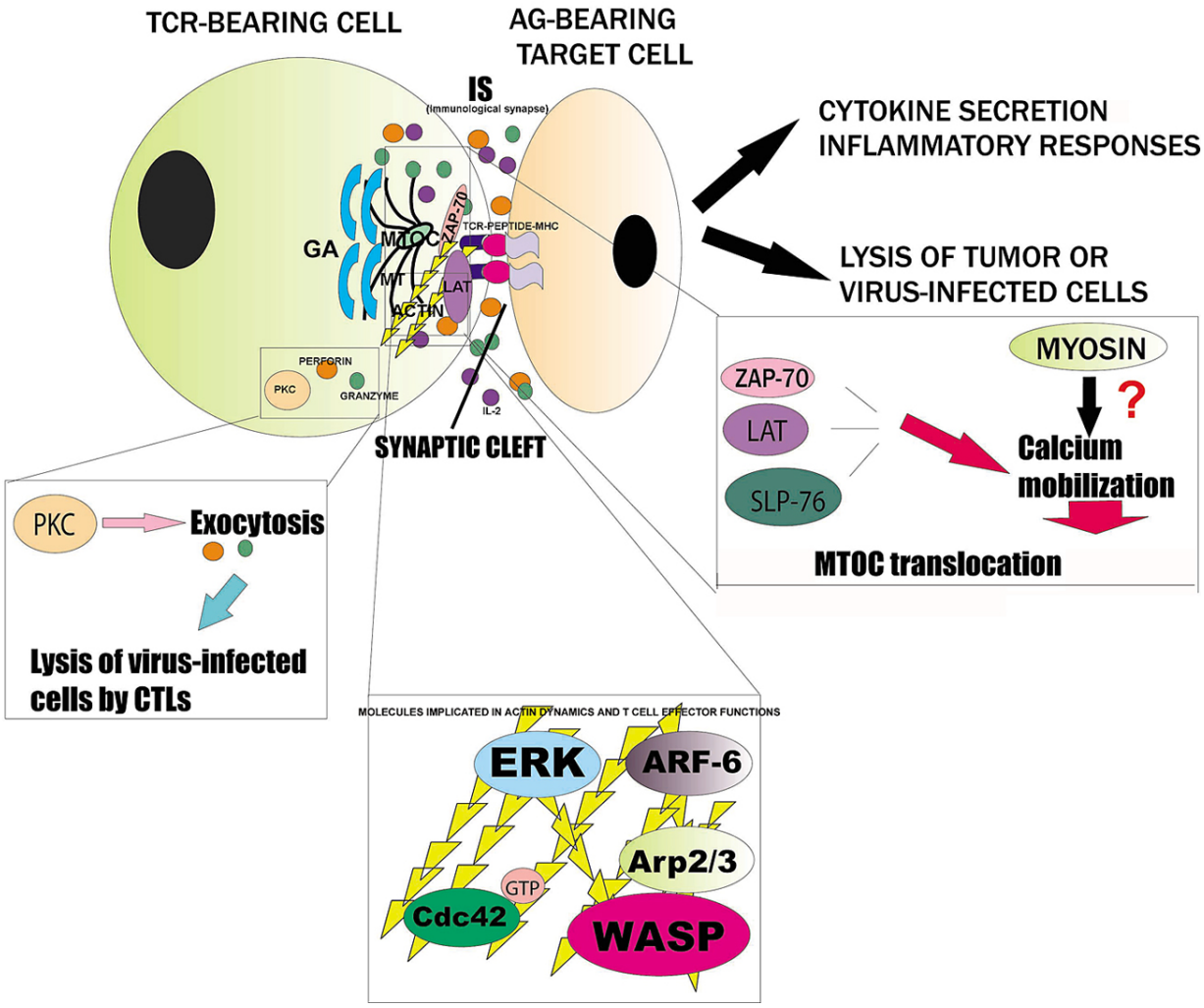

Figure 3. Microtubular network and actomyosin cytoskeleton in effector functions of T cells. During the effector activity of T cells, polarized granule secretion toward the APC occurs. This requires a functional immunological synapse to be formed between the two cells, including the translocation of the MTOC in the T cell. As a result cytokine secretion leads to inflammatory processes or the lysis of tumour or virus-infected cells. The box on the upper right of this figure shows the molecules implicated in MTOC translocation during T cell effector functions. The coordinated activation of ZAP-70, LAT and SLP-76 is required, and leads to sustained calcium mobilization in which myosin is likely to be involved. The participation of PKC in MTOC reorientation in CTLs (cytotoxic T lymphocytes) is shown in the box on the left side of the figure. PKC activation facilitates the exocytosis of granules containing granzyme and perforins, which leads to the lysis of virus-infected cells. The box in the middle depicts different molecules implicated in actin dynamics that are also involved in T cell effector activities, including kinases like ERK (extracellular signal-regulated kinase), GTPases like Cdc42 and ARF-6, and proteins with a role in actin polymerization, like WASP and the Arp2/3 complex.

the actomyosin and microtubular networks is observed and is necessary for granule secretion. It is very likely that the actin cytoskeleton plays an important role in granule exocytosis during target cell killing. Accordingly, inhibitors of actin polymerization abolish changes in CTL shape in response to target cell contact and granule exocytosis. Exposure to such drugs after stimulation with anti-CD3 antibodies also abolishes granule exocytosis (79). Interestingly, F-actin accumulates at activating but not inhibitory synapses in NK cells. In addition, the cytoskeletal linker ezrin and the associated protein CD43 are excluded from the inhibitory, but not from the activating IS of these cells (80). WASp is also required for NK cell cytotoxicity, colocalizing with actin in activating IS formed by NK cells (81).

The MTOC seems to be repositioned by a microtubule-sliding mechanism, concentrating the secretory vesicles at the cell target (6). The mechanisms leading to MTOC reorientation in CTLs and NKs have not been fully elucidated, but several PKC isoforms associated with the MTOC's seem to be implicated in this process. Accordingly, PKC inhibitors can impair this phenomena (82) (Figure 3).

5. PERSPECTIVES

The involvement of cytoskeletal components in T cell activation has been studied extensively. Although it seems evident that the actin framework plays a crucial role in T cell activation, the precise signaling pathways and adapter molecules involved have not been fully characterized. Likewise, while it is clear that the tubulin and actomyosin cytoskeletons participate in T cell effector functions, their exact roles are not well defined. The relationship between the T cell cytoskeletal networks and the processes related to the activation of these immune cells is a very interesting field that requires further exploration.

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Abbreviations: APC: antigen presenting cell, CTL: cytotoxic T lymphocyte, ERM: ezrin-radixin-moesin, GA: Golgi apparatus, ICAM-1: intercellular adhesion molecule-1, IS: immunological synapse, LFA-1: leukocyte function-associated antigen-1 , MHC: major histocompatibility complex MT: microtubule, MTOC: microtubule organizing center, NF-AT: nuclear factor of activated T cells, NK: natural killer, TCR: T cell receptor

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