DOCUMENT SUMMARY

This document is a foundational scientific review from the journal *Cell*, titled "Signaling Takes Shape in the Immune System." It details the complex, multi-step process of T cell activation, focusing on the formation of the "**immunological synapse**"—a highly organized structure at the interface between a T cell and an antigen-presenting cell (APC). The paper explains how this synapse integrates signals from T cell receptors (TCRs), adhesion molecules, and the cytoskeleton to control the immune response. It highlights the importance of molecular patterning, membrane domains (like **GEMs** or lipid rafts), and cytoskeletal dynamics in setting the activation thresholds that prevent both autoimmunity and infection.

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- **Related Docs**: This paper provides a detailed example of the principles of cellular signaling and protein localization discussed in "Translocation and Reversible Localization of Signaling Proteins" and "Cellular Signaling: Pivoting around PDK-1."

FORMATTED CONTENT

Signaling Takes Shape in the Immune System

Michael L. Dustin and Andrew C. Chan *Washington University School of Medicine, St. Louis, Missouri*

Introduction

The adaptive branch of the immune system is built on the principle that the enemy can take any shape or form, but will display different protein sequences from the host. A highly flexible mechanism has evolved to recognize foreign protein segments based on a developmentally programmed series of transient cell-cell synapses between T cells armed with **T cell antigen receptors (TCR)** and **antigen-presenting cells (APC)** decorated with peptide ligands.

The activation of the mature T cell requires interaction of the **TCR** and **MHC-peptide complexes** in a specially organized cell-cell junction between the T cell and the APC that has

been aptly described as an **immunological synapse**. The physical interaction of **TCR** with **MHC-peptide complexes** is unique among signaling systems in that it takes place over a continuum of kinetic parameters with different sensitivity thresholds at different points in development.

> Recent studies have emphasized the importance of cell asymmetry, cytoskeletal dynamics, membrane organization and molecular patterning in setting thresholds for the T cell activation process.

Shortly after contact between the T cell and APC, a bull's-eye pattern forms... Over a period of minutes this bull's-eye inverts resulting in a mature **immunological synapse** characterized by a central group of activated TCRs (the **central supramolecular activation cluster or cSMAC**) that is surrounded by a large ring of adhesion receptors (the **peripheral supramolecular activation cluster or pSMAC**). Maintenance of this stable bull's-eye pattern correlates well with multiple parameters of effective activation of the T cell and the immune response.

Steps of Physiological T Cell Activation

The current paradigm for physiological T cell activation can be broken down into several steps:

1. **T Cell Polarization**: T cells are first polarized and attracted to potential APC by chemoattractants.
2. **Adhesion**: Polarized T cells enter into non-antigen-specific adhesion with the APC. Adhesion receptors bring **TCR** and **MHC** into proximity.
3. **TCR Engagement**: The **TCR** is then engaged by **MHC-peptide complexes**.
4. **Immunological Synapse Formation**: If the interaction exceeds thresholds, signaling and synapse formation are initiated.
5. **Stabilization**: The synapse must be stabilized for several hours for full T cell activation.
6. **Termination**: The synapse is disassembled, and the T cell migrates away.

The Cytoskeletal Renaissance

An important building block of the **immunological synapse** are components of the cytoskeleton. Models for **TCR** collaboration with actin have been profoundly influenced by a recent surge in understanding of how surface receptors are linked to actin polymerization. These studies have identified a common pathway for actin polymerization based on recruitment and activation of the **Arp2/3 complex** to the membrane surface, often involving proteins like **WASP** (the protein deficient in Wiskott-Aldrich syndrome).

Excitement about Membrane Domains

Membrane domains have become a focus in many areas of cell biology. A particularly interesting type of membrane domain termed **membrane rafts**, detergent insoluble domains (**DIGs**), or glycolipid enriched microdomains (**GEMs**) is relatively ordered compared to the bulk of the plasma membrane. This domain is enriched in cholesterol, glycosphingolipids, and a variety of acylated cytoplasmic proteins. Many important molecules in T cell signaling are localized to these domains. One current idea is that the **GEMs** are very small in resting cells and may readily coalesce during signaling in response to receptor crosslinking.

Step 4: TCR Signaling and Immunological Synapse Formation

Engagement of the **TCR** by **MHC-peptide** leads to the assembly of signaling complexes, generates multiple second messengers, and induces cytoskeletal changes required to stop the migration of the T cells (the stop signal). Generation of these second messengers involves the sequential activation of three distinct families of **protein tyrosine kinases (PTKs)**—the **Src**, **Syk**, and **Tec** families.

The enzymatic activities of these three **PTK** families are required to phosphorylate a growing number of linker proteins that function as scaffolds to localize and assemble signaling complexes. Most notable are the **SH2-containing leukocyte protein of 76 kDa (SLP-76)** and the transmembrane **Linker for Activation of T cells (LAT)**.

Step 5: Stabilization

Duration of signaling is also a critical parameter for T cell activation. The maintenance of the **immunological synapse** over many hours may be promoted by molecular changes during its maturation. For example, the recruitment of more rigid lipid rafts (**GEMs**) to the T cell and APC sides of the synapse may contribute to stabilization. Stabilization of phosphotyrosine signals has been associated with the recruitment of **GEMs** to the interface between T cells and anti-TCR coated beads triggered by coligating the costimulatory molecule **CD28**.

> While providing a more rigid platform, the **GEMs** may also help organize competing or antagonistic pathways to sustain **TCR** signaling and maintenance of the immunological synapse. The localization of signaling complexes to these microdomains may sequester them from negative regulatory proteins, such as protein phosphatases including **CD45**.

Conclusions

Focusing on the individual steps of physiological T cell activation allows application of a number of genetic and biochemical studies on model systems to be applied to understanding the integrated process of T cell activation. The determinants of this process appear to regulate the interaction of signals and morphogenic processes such as actin polymerization and myosin II activation in the synapse.

> Is the bull's-eye pattern of the **immunological synapse** (Figure 1B) the supramolecular shape of things to come in signaling? While the concept of the synapse is over a hundred years old, studies in both the nervous system and immune systems on molecular organization of synapses are just beginning. It is likely that many surprises are still in store.