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Review

Synthetic surfaces as artificial antigen presenting cells in the study of T cell receptor triggering and immunological synapse formation

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Abstract

T cell activation occurs when T cell receptors engage peptide-major histocompatibility complex (pMHC) molecules displayed on the surface of antigen presenting cells (APCs). Clustering of TCRs and other receptors in physical patterns at the T–APC interface forms a structure known as an immunological synapse (IS). Studies of the IS are challenging due to the cell–cell contact context of the governing interactions. Model surfaces as synthetic APCs have thus been developed, where the type, quantity, and physical arrangement of ligands displayed to T cells are precisely controlled. These model systems have provided important insights into the structure and function of the IS.

Keywords: T cell activation; Immunological synapse; Supported bilayer; Microfabrication; Nanotechnology

1. Introduction

T cells are activated via binding of their antigen receptors to cognate foreign peptides presented in the cleft of major histocompatibility complex (MHC) molecules at the surface of antigen presenting cells (APCs). One of the intriguing features of T cell activation is the distinct clustering of cell surface receptors and intracellular signaling components which occurs at T cell–APC contacts following the initial engagement of T cell receptors (TCRs) with antigen; this accumulation of receptors is referred to as an immunological synapse (IS). For some T cell–APC interactions, striking patterning of these receptors and signaling components into discrete micro- or submicroscale clusters in the synapse occurs [1,2]. The IS was first characterized in T cell–B cell contacts as a 'bulls-eye' structure composed of TCRs centrally clustered in the interface, surrounded by a concentric ring enriched in the integrin lymphocyte function-associated antigen-1 (LFA-1) [1]. Since this first report, intensive investigation has revealed that receptor clustering in T–APC contacts is hardly a 'one size fits all' affair, and the pattern of receptor clustering in immunological synapses is now known to vary depending on the density and quality of antigen [2–5], the identity and activation state of the APC [6–8], and the maturity and activation state of the T cell [9–14]; other factors will undoubtedly arise as our understanding of T cell triggering on a molecular scale deepens. This variegation is further complicated by the dynamic nature of receptor clustering in the T cell–APC contact during the first minutes to hours of conjugation [2,15,16]. A diversity of functional roles for the IS have been proposed. The synapse may provide biophysical support for antigen receptor signaling [2] or, conversely, controlled extinction of TCR signaling [16,17]; it may serve as a conduit for directed cytokine secretion by the T cell, the APC, or both partners [18,19]; it may also be a site for selective cytokine receptor signaling [20]. The dynamic molecular complexity of live cell–cell contacts has made concrete elucidation of synapse functions a difficult challenge. Thus, despite intensive study, a comprehensive understanding of the factors controlling synapse formation, dissolution, and its functional roles remains an outstanding challenge in immunology [21,22].

Notably, the first report of receptor patterning in the interface of fixed T cell–B cell conjugates by Monks et al. [1] was followed shortly after by a key study utilizing a model of glass-supported lipid bilayers (SLBs) bearing mobile peptide–MHC (pMHC) complexes and adhesion proteins as a surrogate for a live APC, where the dynamics of receptor clustering following T cell engagement with these molecules could be analyzed in detail

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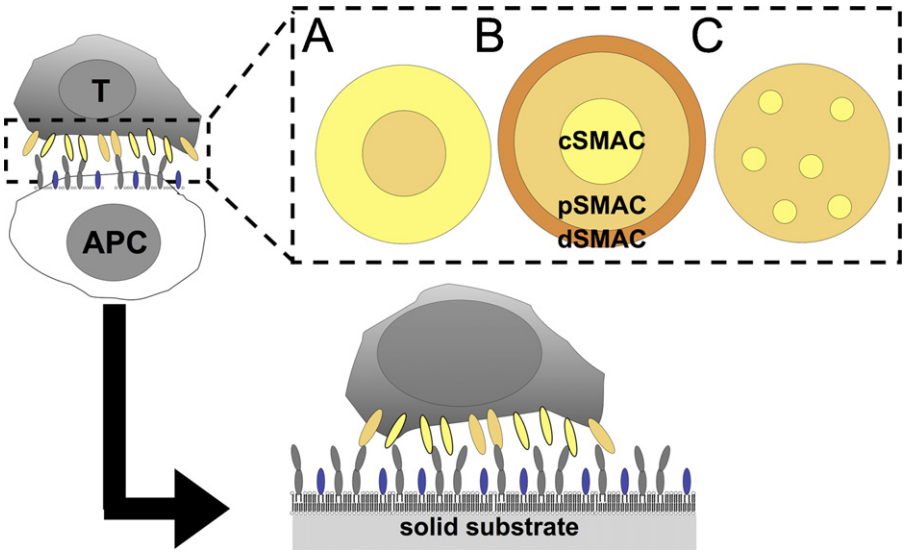

Fig. 1. Immunological synapse formation at T cell–APC and T cell–synthetic surface contacts. Engagement of TCRs with pMHC complexes on the APC surface initiates the assembly of signaling proteins and adhesion receptor pairs at the T–APC junction. Viewed *en face*, a peripheral ring of TCR enrichment surrounding a central cluster of adhesion receptors such as LFA-1 forms in the earliest moments following T–APC contact (A). This early or 'immature' synapse then inverts to form a 'mature' synapse composed of a central supramolecular activation cluster (cSMAC) surrounded by a peripheral supramolecular activation cluster (pSMAC) and distal supramolecular activation cluster (dSMAC) (B). TCRs and signaling components are enriched in the cSMAC, while adhesion receptors are preferentially segregated to the pSMAC. Depending on the status of the T cell and type of APC, other patterns may form, such as a multifocal synapse (C). Replacement of the live APC with a planar synthetic surface displaying reconstituted APC ligands allows the role of ligand composition, areal density, and clustering to be probed in detail.

[2] (Fig. 1). Synthetic surfaces as 'artificial APCs' for the study of T cell triggering have thus played a significant role in dissecting the structure and function of the immunological synapse (IS) since its discovery [2,23,24]. Synthetic surface models provide several advantages that have aided the analysis of these interactions: first, restriction of receptor binding events between the T cell and model surface to a quasi-two-dimensional plane enables greater spatio-temporal resolution of events occurring during T cell recognition via optical microscopy. New high-resolution imaging techniques such as total internal reflection microscopy, which require a flat surface for imaging, are providing exciting new insights into the earliest events in T cell triggering [23,25–27]. Second, key parameters such as ligand density and composition of the 'APC' can be readily varied to systematically examine their effects on synapse formation and T cell stimulation [2,28]. Finally, surface fabrication techniques developed by physical scientists can be used to control the spatial distribution and mobility of ligands displayed from synthetic substrates [29,30]. Such micro/nanofabrication techniques have been successful in addressing a number of key problems in other areas of cell biology by allowing precise control of interactions between cells and extracellular ligands that cannot be achieved by conventional approaches [31–34].

In this review, we will briefly summarize data concerning the structure and functions of the immunological synapse, and discuss several types of model surface systems developed for studies of the structure and dynamics of receptor/cytoplasmic component patterning in the immunological synapse. We will outline the methodologies used, highlight several of the key findings provided by these model systems to date, and summarize challenges that may be tackled using this approach to T cell biology in the near future.

2. T cell antigen recognition and immunological synapse formation

A number of excellent in-depth reviews of various aspects of IS structure and function have appeared recently [21,22,35–38], thus we will focus here on a basic description relevant for discussion of the model systems described in the following sections. TCR triggering by engagement with agonist pMHC at the leading edge of a migrating T cell leads to many immediate downstream events including T cell arrest [39], calcium mobilization [40,41], and immunological synapse formation [1,2]. Three dimensional microscale clustering of receptors and cytoplasmic components at T–APC contacts into a clear 'bull's-eye' pattern, sometimes termed a 'mature' synapse (Fig. 1) was first described for T cells interacting with antigen-pulsed B cells using 3D confocal microscopy [1]. In the mature synapse, TCRs colocalize with protein kinase C-θ (PKC-θ) at the center of the contact, forming a central supramolecular activation cluster (cSMAC), while adhesion receptors such as LFA-1 and VLA-4 as well as the intracellular adaptor protein talin are clustered in a concentric ring, the peripheral SMAC (pSMAC) (Fig. 1A) [42]. An accumulation of large glycoproteins such as CD43, CD44, and CD45 concentrically peripheral to the pSMAC has been termed the distal SMAC (dSMAC) [43].

Since the initial 'bull's eye' structure (Fig. 1) was described for T cell–B cell synapses, studies examining T cell–APC contacts in a variety of systems have reported a diverse array of synapse structures depending on the experimental setting: for example, immature T cells (thymocytes) form dynamic multifocal synapses (Fig. 1) [9,10], and dendritic cells have been reported to exhibit multifocal synapses predominantly over single well-defined cSMACs [6,11]. The dynamics of synapse