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Which Lymphoid Cells Express MHC Class II Antigens; Are TCRs Encoded within the MHC?

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The report by Sachs and Cone (1) is an important historical paper because it correctly demonstrated that serologically detected class II MHC Ags are expressed on B cells and not T cells. The paper came at an incredibly exciting time in science, because the gene products encoded within a central region of the mouse MHC had very recently been reported to determine the outcome of different immune functions, namely 1) responses to synthetic peptides and other Ags (2, 3); 2) susceptibility to viruses (4); 3) mixed lymphocyte responses (5); and 4) graft-versus-host reactions (6). Based on the genetic mapping of these immune functions, this central region of the mouse MHC was designated the Ir, or I, region. Furthermore, because each of these immune functions was known to involve thymocyte-derived cells, it was widely speculated that the Ir region encoded recognition structures on T cells for Ag, that is, the yet-to-be-defined TCRs. Accordingly, it was speculated by Dr. Jan Klein (7) that the discovery of a new class of T cell recognition structures encoded within the MHC would have an enormous impact on modern immunology. Conceptually, it was reasonable in 1973 to speculate that the MHC encoded T cell recognition structures, because MHC restriction, determinant selection, and Ag presentation were all yet to be defined.

Of note, the partitioning of the MHC into gene products at the time of the Sachs and Cone contribution (1) was based on comparisons of different mouse strains with genetic crossovers between MHC-encoded loci as determined typically using serological markers. Using this approach, the mouse MHC was initially subdivided into K, Ir, S, and D regions, such that the K and D regions encoded the major transplantation Ags as detected by allograft rejection or alloantisera, the Ir region encoded the determinants of the aforementioned four immune T cell functions, and the S region encoded complement components (8). Based on a lack of knowledge of the molecular basis of these serological and functional assays, it was proposed that genetically mapped loci be classified as either serologically defined or lymphocyte defined (9). Using this obfuscating nomenclature, the Ir region in 1973 contained lymphocyte-defined and not serologically defined determinants. To determine whether Abs could be generated to Ir region-encoded gene products, several laboratories used intra-MHC recombinant mouse strains, most of which were generated by the laboratories of Drs. George Snell, Jack Stimpfling, or Donald Shreffler. Three different laboratories published papers in 1973 reporting detection of Ags encoded within the Ir region of the MHC. Jan Klein and colleagues (7, 10) reported in Science and Journal of Experimental Medicine the characterization of antisera raised by immunizing Ir region-disparate mouse strains with lymphoid cells. They designated their Ag Ir-1.1 based on their reported detection of Ir-1.1 “only on thymus-derived T lymphocytes.” In 1973 as well, Shreffler’s laboratory used a similar approach and reported that their antisera to Ags encoded within the Ir region were reactive predominantly with lymph node cells (11). This group tentatively designated their Ag Lna, for lymph node Ag. In striking contrast to these other reports, Sachs and Cone (1) reported in this same year that their antisera to gene products encoded within the Ir region detected B cells and not T cells. They got it right!

The first approach taken by Sachs and Cone was to raise heterologous antisera by immunizing Fischer rats with B10.D2 (H-2d) mouse lymphocytes. When tested for reactivity on B10.D2 lymphocytes in complement-mediated cytotoxicity assays, their heterologous antisera lysed >80% of the cells, consistent with its inclusion of Ab to MHC class I molecules. However, unexpectedly, when they tested their heterologous antisera to Ags encoded within the major transplantation Ags expressed on B cells. Thus the cross-reactive Ags expressed preferentially on B cells. They provisionally called these novel Ags β. Using intra-MHC recombinant mouse strains, they then mapped genes determining β expression within or near the Ir region. Importantly, Sachs and Cone also reported the detection of Ab with anti-β activity in alloantisera. Their findings can be explained retrospectively by the fact that I-A proteins of the d and b haplotypes are more serologically cross-reactive than their respective K\textsuperscript{b} and K\textsuperscript{d} class I proteins. In any case, Cone and Sachs correctly determined that Abs to MHC class II proteins detect predominantly B cells and not T cells, a finding corroborated in 1974 by Hammerling et al. (12). It must be noted that these observations were made before modern day methods of mAb production and identification of specific immune cell types by cytometry. Using today’s approaches, it is now clear that MHC class II proteins are highly expressed on other professional APCs (e.g., dendritic cells and macrophages) in addition to B cells. Furthermore, Ab blocking studies and genetic approaches have provided unequivocal evidence that serologically detected class II molecules on APCs control Ag-specific immune responses of CD4\textsuperscript{T} T cells.
In conclusion, the B cell expression of MHC class II discovered first by Sachs and Cone (1), in combination with the elegant genetic mapping studies of the Shreffler, Klein, and McDevitt laboratories (7, 10, 11), caused a paradigm shift. Whereas the bias in 1973 was that the Ir region encoded TCRs for Ags, the finding of MHC class II expression on non-T cells laid the foundation for subsequent discoveries that MHC class II proteins bind peptides for presentation by APCs to CD4+ T cells (13).

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References