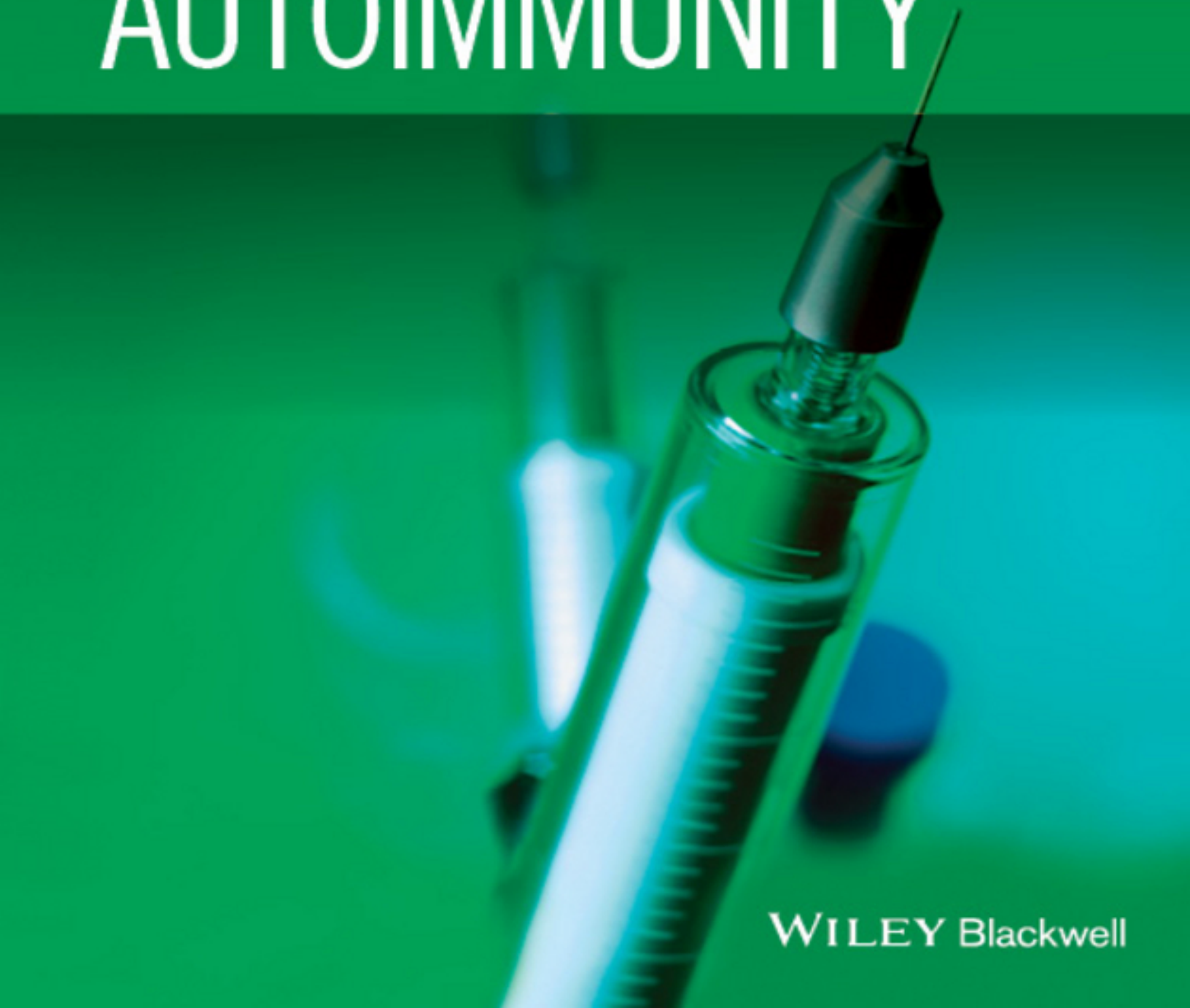
Edited by
Yehuda Shoenfeld, Nancy Agmon-Levin
and Lucija Tomljenovic

VACCINES & AUTOIMMUNITY



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Chapter 6: Genetics and Vaccinology

Figure 6.1 Map of the human HLA. The region is conventionally divided into three subregions: the class I, II, and III regions. Each contains numerous genes – only a few of the most relevant are shown here. Abbreviations: *TAPBP*, Tapasin; *LMP1* and *LMP2*, large multifunctional proteases 1 and 2; *TAP1* and *TAP2*, transporter associated with antigen processing 1 and 2; *C2*, *C4A*, and *C4B*, complement components 2, 4A, and 4B; *BF*, complement factor B; *HSPA1A* and *HSPA1B*, heat-shock protein 1A A-type and B-type; *HSPA1L*, heat-shock protein 1A-like; *LTA* and *LTB*, lymphotoxins A and B; *TNFA*, tumor necrosis factor α; and *MICA* and *MICB*, major histocompatibility complex class I chain genes A and B.

Figure 6.2 Antigen processing by HLA class I and II molecules. (a) Class I antigen processing and presentation occurs when proteins in the cytosol are degraded by the proteosome into small peptides and then are transported by transporter associated with antigen processing (TAP) into the endoplasmic reticulum (ER) lumen. HLA class I molecules are synthesized, translocated, and assembled into the lumen of the ER, where they load the peptide; HLA class I–peptide complexes then leave the ER and move through the Golgi apparatus to the plasma membrane, where they present the joined peptide to the T cell receptor (TCR) of $CD8^{+}$ T cells. (b) Class II presentation occurs when extracellular proteins are phagocytized and then degraded into small peptides. These peptides are then sorted into vesicles, where they interact with the HLA class II molecules. HLA class II α and β chains, class II-associated invariant peptide (CLIP), and the invariant chain (Ii) molecules

that recognize the H1N1 epitope and then migrate to the CNS, where they recognize an antigen specific to orexin-producing neurons (crossreactivity). Activation of crossreactive T cells results in the release of cytokines and chemokines, which recruit and activate macrophages, mediating self-tissue damage. The subsequent release of orexin self-antigen and its uptake by antigen-presenting cells (APCs) perpetuates narcolepsy. (ii) Crosslink of the MHC and TCR molecules and activation of the cytotoxic T cells, which are autoreactive and specific towards orexin-producing neurons, by H1N1 antigens or Pandemrix vaccine. (iii) Molecular mimicry involving B cells and antibody-mediated disease. This could target TRIB2 as a crossreactive antigen. It would require signals from activated T cells (T cell help). (iv) Bystander activation of resting autoreactive B and T cells. This could result from general immune activation, independent of specific antigens. Current results in narcolepsy research point towards a T cell mechanism. Abbreviations: APC, antigen-presenting cell; BBB, blood–brain barrier; CNS, central nervous system; H1N1, H1N1 influenza A virus or epitopes from adjuvant vaccines; MHC, major histocompatibility complex; TCR, T cell receptor; TRIB2, Tribbles homolog 2. Reprinted and modified from Singh, A.K., Mahlios, J., and Mignot, E. (2013). Genetic association, seasonal infections and autoimmune basis of narcolepsy. *J Autoimmun*, **43**: 26–36. Copyright (2013) with permission from Elsevier.

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