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Peyer’s Patches as the Inductive Site for IgA Responses

Jiri Mestecky and Charles O. Elson1

The seminal publication by Craig and Cebra (1) had a remarkable impact not only on the field of mucosal immunology but also on the entire immunological literature. The potential of intestinal lymphoepithelial organs called Peyer’s patches to restore the immune system of lethally irradiated mice had been previously noted by Jacobson et al. (2), who found that the shielding of a single Peyer’s patch during x-ray exposure restored immunological functions and prevented death of the mice. This finding provided evidence for the migration of lymphocytes and other precursor cells from Peyer’s patches to the peripheral lymphoid organs. However, the phenotypes of Peyer’s patch-derived cells were not known.

Craig and Cebra (1) focused their experiments on the restoration of the mucosal immune system to explore and explain the observed preponderance of IgA-producing cells in mucosal tissues, particularly the gut. The repopulating potential of lymphocytes obtained from Peyer’s patches as compared with lymph nodes or peripheral blood of a donor was evaluated by the transfer of these cells into lethally irradiated recipient rabbits. To ensure that the cells found in a recipient’s lymphoid tissues were of donor origin, cells from rabbits homoygous for the L chain b5 allotype were transferred by i.v. injection into recipients homozygous for the b4 allotype. By containing various lymphoid tissues with reagents specific for rabbit α and γ H chains and L chain b4/b5 allotypes, donor-derived cells were reliably recognized. Craig and Cebra clearly and convincingly demonstrated that the recipients’ intestinal lamina propria contained large numbers and clusters of IgA-producing cells of donor origin when Peyer’s patches were used as a source. In sharp contrast, the transfer of lymph node-derived lymphocytes resulted in a dominant repopulation of spleens in recipient animals by IgG-producing cells. Thus, Craig and Cebra proposed “... that the function of the Peyer’s patches in the immune system is to furnish IgA precursor cells or antigen reactive cells to the lamina propria of the small intestine, the mesenteric lymph nodes, and perhaps to other lymphoid tissues and secretory glands as well.” Craig and Cebra also predicted that this clearly demonstrable difference in the repopulation potential of Peyer’s patch- or lymph node-derived cells is due to specific “homing” to relevant lymphoid organs rather than to Ag-driven or random seeding followed by local selective proliferation of cells. Note that this was postulated several years before the homing receptors and corresponding ligands expressed on endothelial cells and lymphoid cells were discovered. Craig and Cebra’s paper extended and provided an anatomic explanation to earlier publications of Griscelli et al. (3) and Hall and Smith (4), which indicated that lymphoblasts from the thoracic duct localized primarily to the intestine. Subsequently, Cebra and his numerous coworkers published a series of related articles concerning the induction of specific IgA responses to viral and bacterial Ags, using the Thirty-Vella intestinal loop model to provide additional evidence and to exploit the potential applications of their findings to vaccinology. Peyer’s patches and related intestinal lymphoid follicles were subsequently named gut-associated lymphoid tissue or GALT.

Shortly after these publications, several investigators extended these findings to lymphoepithelial structures in the respiratory tract (bronchus-associated lymphoid tissues) (5, 6) as inductive sites, as well as to salivary glands, lactating mammary glands, and female genital tract tissues as effector sites (for historical review, see Ref. 7). Ultimately, Bienvenuto (8) concluded that “the bronchus- and gut-associated lymphoid tissues might be a part of a more universal mucosal lymphoid system,” and in 1974 coined the term common mucosal immunologic system.

Studies of the origin, migration, and homing of lymphoid cells from the inductive to the effector sites were of basic importance for parallel attempts to induce specific immune responses in mucosal tissues and glands anatomically remote from the original mucosal site of Ag encounter. These studies also stimulated extensive and intensive investigations seeking to exploit these principles in the design of novel, mucosally-administered vaccines (for reviews, see Refs. 7 and 9).

In the age of quick computer searches, seminal papers are often overlooked or misinterpreted. We encourage attentive researchers to read this paper of luminous clarity and exceptional importance. We acknowledge the major advance it represented to the field and, in so doing, pay tribute to our late, esteemed colleague, Dr. John J. Cebra.

References

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