MIIM30003 MST01 Mock Paper

MULTIPLE CHOICE

MCQ1) Lymphocytes may upregulate homing markers to direct themselves to certain tissues. Which option correctly identifies the pair of homing marker and tissue-specific receptor?

A. α4β7 (TC & BC) & CCL28 (Colonic Epithelial Cells)
B. CCR9 (BC) & CCL28 (Colonic Epithelial Cells)
C. CCL28 (Colonic Epithelial Cells) & E-Cadherin (Epithelial Cells)
D. CCR10 (BC) & CCL28 (Colonic Epithelial Cells)

MCQ2) Membrane-bound BAFF can be cleaved to become a Soluble BAFF trimer but it can also form a virus-like capsid structure called a 60-mer via oligomerization. Another membrane bound ligand is the APRIL trimer that is cleaved and can be bound to HSPG where the aggregation of APRIL trimers can achieve cross-linking of ligands to concentrate the signal. The corresponding B Cell Receptors to the previously mentioned ligands include BAFFR, BCMA, and TACI. Which option correctly identifies the receptor, its corresponding ligand, and the function of the interaction?

A. BAFF-R & BAFF for Plasma Cell Survival
B. BAFF-R & BAFF for Immature BC Survival & Maturation
C. BCMA & BAFF/sAPRIL for T Cell-Independent Antibody Responses, B Cell Regulation, Class-Switch Recombination
D. TACI & sAPRIL for Immature BC Survival & Maturation

MCQ3) Autoimmune Diseases can be categorised into AutoAb-Driven, TC & BC-Driven, and Dominantly TC-Driven. In order to analyse the mechanisms of these autoimmune diseases, researchers employ animal models. Which option correctly pairs the autoimmune disease with the animal model?

A. SLE & Collagen-Induced Arthritis Mice Model
B. MS (Multiple Sclerosis) & EAE (Experimental Autoimmune Encephalomyelitis)
C. Crohn's Disease & $TACI^{-/-}$ Mice Model
D. Type 1 Diabetes & Irritant-Induced IBD Mice Model

MCQ Solutions

MCQ 1- Solution Pathway

α4β7 is expressed on TCs & BCs and is a homing molecule that directs the lymphocytes to the HEV on the basis of the MAdCAM-1 receptor. Thus A is wrong. CCR9 is expressed on both TCs & BCs and allows for migration to the Small Intestinal Epithelial Cells via CCL25. Thus, B is wrong. E-Cadherin expressed on epithelial cells is paired up with CD103 (AKA alphaEbeta7) Note that this interaction represents an induction in effector sites. Thus C is also incorrect. (Can you recall another TC subset that predominantly expresses this receptor? $CD8^{+}CD103^{+}$ T_{RM} will express CD103 to localise at tissues.) This leaves the correct answer as D.

MCQ 2- Solution Pathway

BAFF-R & BAFF allows for immature BC survival and maturation. Thus B is correct. BCMA (& BAFF/sAPRIL) is important for plasma cell survival. In contrast, TACI (& BAFF/sAPRIL) allows for T Cell-Independent Antibody Responses, BC Regulation, Class-Switch Recombination.

MCQ3- Solution Pathway

The Collagen-Induced Arthritis Mice Model is used for the study of Rheumatoid Arthritis. The generation of the mouse line involves (i) D0 immunization with Type II Collagen/CFA, (ii) D18 Booster, (iii) Arthritis Development 4-10 days later. It should be noted that it tends to work better in mice with a DBA background as the MHC genetic specificity is important to present the collagen peptide in a specific manner that breaks tolerance. In addition, the correct experimental model in mice for SLE is the BAFF Transgenic Mice which overexpress soluble BAFF by hepatocytes. In fact, patients with SLE and other autoimmune disease exhibit elevated levels of BAFF. Intestinally, this mice model was used in conjunction with a $TACI^{-/-}$ mutation to show that when WT (Control) & $TACI^{-/-}$ BM of the mice model were transferred to recipient mice, WT resulted in the transfer of disease and pathology while the mice receiving the $TACI^{-/-}$ population demonstrated no disease which suggests TACI is involved in SLE. Thus, A is incorrect. Crohn's Disease can be studied via the Irritant-Induced IBD Mice Model where different irritants to induce inflammation of the intestine by destroying the gut epithelial lining and disturbing the mucosal membrane. Thus, C is wrong. The mouse model of Type 1 Diabetes is the Non-Obese Diabetic (NOD) Mice Model where the mice spontaneously develop TC-mediated Insulitis followed by diabetes (in adult mice). Hence, D is incorrect. B is the correct solution.

SHORT ANSWER

SAQ1) What are the four possible outcomes for self-reactive B cells? What determines the outcome?

SAQ2) What are the properties of the cells which survive?

SAQ3) What are the sources of tissue-specific antigen in the thymus and how are TSAs presented to thymocytes**?**

SAQ4) *How does a 'resting' environment vs an 'infectious' environment affect interactions between dendritic cells and T cells? What are the downstream effects of these differing cell-cell interactions?*

SAQ5) Angioedema and anaphylaxis are not features of coeliac disease. *What are they features of? Why does iron deficiency occur? Why might the risk of other autoimmune diseases be increased in coeliac disease patients**?***

SHORT ANSWER- SOLUTIONS

SAQ1*- solution pathway*
1.Deletion-membrane bound antigen that crosslinks multiple BCRs (i.e. there must be high affinity with the self-Ag, low affinity binding which is not detected by BCRs may allow for autoreactive BCs to escape NS.)
2.Receptor Editing (Receptor Editing occurs when one of the chains is not configured properly and can undergo another round of rearrangement to generate a non self-reactive BCR.)
3. Anergy- soluble antigen that doesn't crosslink BCRs. The phenotype of anergic cells: low CXCR5(cannot gain access to the follicles to receive survival signals i.e. follicular exclusion), low expression of IgM(less likely to encounter and internalise their cognate antigen), low BAFFR (cannot receive BAFF which is important for survival in mature B cells), failure to upregulate co-stimulatory molecules (cannot receive T cell help)
4. Ignorance (Ignorance occurs when the BCs are not aware of their self-Ag due to reasons such as immune privileged sites or barriers that prevent access to the self-Ag.)

SAQ2- *solution pathway*
Cells that survive tend not to react strongly towards self antigens. (Note that in the case of autoreactive BCs, they are able to survive the NS process due to low affinity BCRs which do not elicit a strong enough signal for death.)

SAQ3 *solution pathway*

Sources:
1. From the circulation
2. From mTECs (they express AIRE): They mature and eventually die (self-induced apoptosis), upon dying, they secrete chemokines XCL1, which attract the DCs in the cortex

to them. These DCs now have lots of TSAs and can present them to thymocytes. Note that self-Ags can also be presented on cTEC and mDCs in addition to mTECs and the circulation. (Note that AIRE is responsible for regulating apoptosis. In fact, a mutation in AIRE leads to the aggregation of mature mTECs in the thymus but also results in APECED. In addition, it should be noted that AIRE does not regulate all of the TSAs. We know these two facts from AIRE KO studies.)

***SAQ4**- solution pathway*
Resting environment: no co-stimulatory molecules (signal 2), strongly downregulate IL-7R, low IL-2 production, no effector function, upregulation of inhibitory molecules (e.g. PD-1) to suppress TCs, upregulation in Bim (pro-apoptotic) for death, downregulation in Bcl-2 (pro-survival).

Infectious environment: upregulation of co-stimulatory molecules by the DC, IL-7R downregulation happens, but to a lesser extent; increased IL-2 production; Acquire effector function; upregulation of $Bcl X_L$ (pro-survival); no upregulation of Bim.

IL-15 and IL-21 play important roles in the development of intestinal lesions in coeliac disease. Describe the model of how the various cells and cytokines interact to cause villous atrophy.

Th1 cells specific for gliadin peptide secrete IL-gamma, IL-21. The microbiota cause cells to produce IL-15. The production of IL-15 specifically suppresses Tregs and hence this prevents the suppression of Th1 that are driving the disease. IL-21 specifically is involved in providing BC help which may amplify and sustain the autoimmune response. In addition, the Tg2-specific BCs of which produce Tg2 Abs can exert cytopathic effects (e.g. issues with placenta formation). Collectively, these cytokines cause intra-epithelial lymphocytes to develop NK-like characteristics, ie. the ability to lyse the epithelial cells that express stress markers like MICA.

SAQ5- *Solution pathway*

Angioedema and anaphylaxis are features of allergies, especially IgE-mediated food allergies.
Iron deficiency occurs as a result of villous atrophy- reduced capacity to absorb iron by the villi.
Patients who have coeliac disease are also at greater risk of having 'other' autoimmune diseases because of their genetic profile. Certain genes that increase one's risk of coeliac disease also overlap with ones that increase one's risk of having SLE, Type 1 diabetes, multiple sclerosis.