ANTIBODIES 2
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OR.101. Secretory IgA and the Polymeric Ig Receptor Affect Mucosal Homeostasis and Susceptibility to Autoimmune Disease in a NOD Mouse Model

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Susceptibility to Type 1 Diabetes (T1D) is determined by a complex interaction between genetic and environmental factors. Gastrointestinal permeability, inflammation, diet and infection are among several factors implicating the mucosal immune system as the pivotal environmental determinant of susceptibility. Recent reports show that changes in commensal flora and innate signaling through MyD88 can drastically effect the development of β-cell specific autoimmunity in the non-obese diabetic (NOD) mouse model of T1D (Nature 2008;455:1109). Given the role of secretory antibodies and the polymeric Immunoglobulin Receptor (pIgR) in maintenance of mucosal homeostasis and protection from infection, we postulated that the incidence of diabetes in NOD mice lacking secretory antibody would be altered. In order to investigate this possibility, a disrupted gene encoding the pIgR was crossed onto the NOD mouse strain to create NOD.B6 pIgR knockout mice. We show here that the pIgR knockout mutation significantly reduces the incidence of T1D in male and female NOD mice in comparison to wild type NOD mice. We are currently analyzing the activation of auto-reactive T cells in mesenteric and pancreatic lymph nodes to determine if systemic suppression of immune activation occurs in NOD.pIgR knockout mice. Thus, this study provides a model to understand the link between autoimmunity, the mucosal immune system and the environment.

OR.102. Influence of IgA Expression on B Cell Homeostasis

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Individuals with selective IgA deficiency are competent in producing IgG antibodies but often suffer from recurrent respiratory infections with encapsulated bacteria. We examined the immunological basis for this susceptibility using an IgA deficient (IgA-KO) mouse model. Following i.m. vaccination, wild type and IgA-KO mice produced similar levels of all antibody isotypes (except IgA) against protein antigens. However, IgA-KO mice were severely defective in producing IgG antibodies against polysaccharides and polysaccharides conjugated to carrier proteins. Administration of IL-12 as an adjuvant during vaccination increased IgG antibody levels in both wild-type and IgA KO mice to the same degree, suggesting a quantitative rather than qualitative defect in polysaccharide-responsive cells in IgA-KO mice. Indeed, the peritoneal cavity of IgA KO mice contained significantly fewer B-1a cells, the cell type thought to be primarily responsible for antibody responses to polysaccharides. Interestingly, significantly fewer B cells were also found in mucosal tissues of IgA KO mice. Since a large percentage of mucosal B cells are of B-1 cell origin, we are currently investigating the influence of IgA on homeostasis and trafficking of B1 cells. These results could explain the frequent failure of conjugate vaccines to induce protective immunity in IgA-deficient patients. (Supported by NIH Grant AI041715).

OR.103. Bystander Activation of Mucosal IgA Memory Following Parenteral Vaccination in Humans

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Recent vaccine efforts direct immunization through mucosa tissues, to generate mucosal IgA against infections pathogens. However problems remain related to booster immunization and development of long term memory IgA responses by humans. Parenteral immunization could provide either antigen-specific or bystander booster immunization, and thereby generate stronger, long term memory for mucosal IgA antibody. Bystander IgG recall responses have been demonstrated for parenteral immunization. We have examined the IgA antibody response in blood of human subjects immunized with a common parental vaccine containing tetanus and pertussis toxoids. The pre-plasma cell fraction of blood B cells was isolated before immunization, at day 6 and at day 21, from normal healthy subjects. Total IgA, IgG and antibodies of these isotypes against polio, HSV and TT produced by the pre-plasma cells were counted in ELISPOT assays. All subjects responded with increased numbers of IgA and IgG producing cells on day 6. The IgG secreting cells were largely accounted for by the recall response to TT. In a large fraction of subjects, substantial numbers of IgA and/or IgG producing cells were found on day 6, with specificity for HSV and polio antigens. Response to TT was only IgG. A majority of the responding IgA pre-plasma cells expressed CCR10, and the IgA produced by these cells was predominantly polymeric. We conclude that a by-stander booster effect is provided by parental immunization, that allows generation of pre-plasma cells capable of seeding mucosal tissues with polymeric IgA secreting cells against common mucosal pathogens.

OR.104. Biosynthesis of O-glycans on Human IgA1

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Glycans participate in biologically important functions of IgA1, such as receptor binding, exclusion of microorganisms, complement activation, and catabolism. Human circulatory IgA1 has hinge-region O-glycans composed of N-acetylgalactosamine

(GalNAc) and galactose (Gal); Gal may be sialylated with α2,3-linked sialic acid and/or GalNAc with α2,6-linked sialic acid. To characterize IgA1 O-glycosylation, we EBV-immortalized peripheral blood lymphocytes and subcloned IgA1-secreting cells. We analyzed the composition of O-linked glycans and their sites of attachment on the hinge region of IgA1 secreted by these cells and characterized the corresponding glycosylation pathways. IgA1-producing cells from some individuals had an abnormality resulting in Gal-deficiency of some O-glycans on IgA1. This glycosylation aberrancy was not generalized but restricted to only some of the O-glycans on polymeric but not on monomeric IgA1, and was due to an imbalance in activities of two key glycosyltransferases. Activity of β1,3-galactosyltranferase (C1GalT1) was reduced while activity of α2,6-GalNAc-specific sialyltransferase (ST6GalNAcII) was elevated, resulting in production of IgA1 with decreased content of Gal and increased content of sialylated GalNAc residues. Our data indicated that this phenotype is determined genetically and further affected by environmental factors through specific cytokines.