

REVIEW ARTICLE

(Xeno)estrogen Regulation of Food Allergy

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Food allergy and other types of allergies are becoming epidemic in both the developed and developing countries. A large amount of information is available in literature that (xeno)estrogens can regulate the immune response in general, and the development of allergy in particular; however, the effect of (xeno)estrogens on food allergy is basically unknown. With increasing use of xenobiotics worldwide, chemicals with estrogenic activity have been accumulating in our environment. This review has summarized the current literature relating to the topic (xeno)estrogen regulation of food allergy. The effect of (xeno)estrogens on enterocytes, proteases for protein hydrolysis, dendritic cells and T-regulatory cells in the gastrointestinal tract has been discussed. Finally, considering the current confusion in literature regarding the effect of phytoestrogen genistein on the immune system, a brief discussion has been included for its effect on T_H1 - T_H2 polarization, and possibly food allergy in its relation to windows of exposure. Sufficient evidences exist to support the notion that (xeno)estrogens can regulate food allergy, with the developmental periods more sensitive. Further clinical and animal studies are needed to determine the causal relationship between the exposure of (xeno)estrogens and incidence of food allergy, and the underlying mechanisms.

Keywords Food allergy, gastrointestinal tract, IgE, genistein, (xeno)estrogens, enterocytes, dendritic cells, T-regulatory cells

INTRODUCTION

Food allergy is becoming a major public health problem that affects 3–4% of adults and 6–8% of children in the United States, and is increasing in prevalence (Gizzarelli et al., 2006). This is demonstrated by the increase in emergency room visits due to food allergy, which have increased by a factor of 6 over a decade, as well as an increased incidence of anaphylaxis caused by food allergy (de Blok et al., 2007). Food allergy often appears in early stages of the allergic reactions, and is a significant predictor for

the development of asthma (Bener et al., 2005); however, asthma alone as a manifestation of a food allergy is rare and atypical (Ozol and Mete, 2008). The most common food allergies in adults are the following foods or food groups: cow's milk, eggs, fish, wheat, peanuts, soybean, crustacea (shrimp, crab and lobster), tree nuts (almond, hazel and walnut) and sesame seeds, and in children, the most common food allergens are present in milk, eggs, and peanuts (Lied, 2007).

Food allergies have several distinct clinical and immunologic entities (Veres et al., 2003). These entities can be classified into those that are IgE mediated and those that are non-IgE mediated, a cell-mediated immunologic reaction involving both immune complex formation and complement deposition. IgE-mediated reactions are typically rapid in onset, mostly involve the skin, and may lead to anaphylaxis; whereas non-IgE-mediated disorders become evident hours to days after allergen ingestion, and mostly manifest in the gastrointestinal (GI) tract. IgE-mediated GI disorders include GI anaphylaxis and oral allergy syndrome. Non-IgE-mediated GI allergic disorders include food protein-induced enterocolitis, proctocolitis and enteropathy. Some GI diseases, such as eosinophilic esophagitis and gastroenteritis, involve both IgE and non-IgE mediated mechanisms (Chehade, 2007). In either case, various inflammatory cells and their mediators play a role in their immunopathogenesis. Activation of lymphocytes and the recruitment of eosinophils and mast cells are the key events of many of these diseases (Takayama et al., 2007).

(Xeno)estrogen, Immune System and Allergy

Immune responses are sexually dimorphic in both the type and magnitude (Lamason et al., 2006). During their reproductive years, females have more vigorous cellular and humoral immune responses than males as evidenced by higher immunoglobulin concentrations and a greater ability to reject tumors and homografts. Estrogen appears to play a central role in mediating these effects. Estrogen is known to have biphasic effects: while estrogen at the levels of the menstrual cycle is stimulatory, it suppresses cell-mediated immune responses at higher concentrations, e.g., during pregnancy in which the levels of estrogen are 100 to 1000 times that of cycling females (Kovacs et al., 2002; Ohshima et al., 2007). There has been a significant increase in

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the prevalence of allergic diseases, including food allergies, over the past few decades. Furthermore, there are differences between men and women in the incidence of allergic diseases. Estrogen has been suggested to be involved in progression of diseases such as asthma, allergic rhinitis and dermatitis (Inadera, 2006).

During childhood more boys than girls are affected by asthma (Wjst and Dold, 1997) and atopic dermatitis (Böhme et al., 2001), while this ratio is reversed at puberty when estrogens play a more important role in girls. Many epidemiological studies suggest that women are at increased risks of developing adult-onset asthma and also suffer from more severe asthma than men (Melgert et al., 2007). With the onset of puberty the frequency of hospital admission for asthma is higher among females. A significant positive association between treatment with sex hormones and adult onset asthma in an epidemiological study of more than 100,000 nurses in the USA has also been reported (Troisi et al., 1995).

Prenatal events appear to be crucial in programming the infant immune system. Allergic T-lymphocytes are typically primed *in utero* and subsequently reshaped during postnatal allergen exposure *via* immune deviation, leading to the eventual emergence of stable allergen-specific memory T-lymphocytes that are polarized toward either the T_H1 (normal) or T_H2 (atopic) phenotype (Holt et al., 1999; Ohshima et al., 2007). Neonatal T-lymphocytes have a unique feature that they tend to develop a prolonged primary T_H2 effector function while an impaired T_H1 memory effector function (Rose et al., 2007), which may account for the presence of a high risk 'window' for allergic sensitization in early postnatal life.

Although no direct study has been performed to address the modulatory effect of perinatal estrogen treatment on the development of T_H1/T_H2 response and allergy in human later life, some implications may be obtained from the study of birth order. In a study involving over 11,000 men, Matricardi et al. (1998) have shown that the prevalence of atopy is much higher among first-born men. The possible underlying mechanism is that there is a higher level of free estrogen in first pregnancy as result of a deficit in sex-steroid binding globulin production, which may predispose the first-born offspring toward the T_H2-type immune response (Bernstein et al., 1986; Martin, 2000).

An association of maternal use of oral contraceptive pills before birth with a higher risk of atopic diseases (asthma, allergic rhinitis and atopic eczema) in the offspring compared with children of mothers who had never taken hormonal pills has been reported (Chalubinski and Kowalski, 2006). Additionally, long-lasting immune modulatory effect of neonatal diethylstilbestrol (DES, a synthetic estrogenic compound) treatment has been demonstrated in both human and animal studies (Kalland and Forsberg, 1978; Luster et al., 1979; Ways et al., 1987). In mice, exposure to DES either *in utero* or in the first 5 days after birth diminished the delayed hypersensitivity responses (Kalland and Forsberg, 1978; Luster et al., 1979). However, PHA-induced PBMC proliferation was enhanced in the *in utero* DES-exposed women (Ways et al., 1987). Studies with small

number of DES daughters have also suggested functional alterations in natural killer cells and a hyper-responsive immune system. Autoimmune diseases occur more frequently (about a 2-fold increase) in women with prenatal DES exposure compared with controls. Although it is controversial (Baird et al., 1996), asthma, arthritis, lupus and diabetes mellitus were reported more frequently among individuals with DES exposure (Vingerhoets et al., 1998).

Estrogen not only occurs as natural estrogens, but also as environmental estrogens (xenoestrogens). Environmental estrogens are present in plastics, detergents, diesel exhaust particles (DEP), pesticides and plants (phytoestrogens), such as DDT, polychlorinated biphenyls (PCBs), 4-nonylphenol, 4-octylphenol, 4-nitrophenol, genistein and many others. The concept of estrogenicity of an exogenous chemical is based on the property of these compounds to bind to, or modulate the function of the estrogen receptors (ER α or ER β), and to act subsequently as transcription factors when binding directly to DNA through the estrogen response element. Although both ER α and ER β have been described as nuclear receptors, they are also located in other organelles (e.g., the plasma membrane, cytosol, endoplasmic reticulum and mitochondria), and are able to bind estrogens to trigger rapid actions (Ropero, 2006). By interacting with ERs, the environmental estrogens, like endogenous estrogen, are capable of affecting cells of the immune system. In general, pesticide exposure causes a decrease in cell-mediated immunity and yet an increase in humoral immunity (Crinnion, 2000).

These changes result in a decreased host resistance, and an increase in allergic diseases and certain cancers. The incidence of asthma has been found to be significantly associated with exposure to endocrine active environmental compounds such as carbamate insecticides, *p*, *p*-DDE and PCBs (Senthilselvan et al., 1992; Reichrtova et al., 1999). Exposure to 4-tert-octylphenol, bisphenol A [2,2-(4,4-dihydroxy-diphenol) propane] and nonylphenol has also been reported to enhance interleukin (IL)-4 production in CD4⁺ T-lymphocytes and IgE production in antigen-primed mice (Lee et al., 2003, 2004). Allergic contact dermatitis from bisphenol A exposure has been reported widely (Matthieu et al., 2003; Connolly et al., 2006; Chu et al., 2006). Benzophenone, *p*-octylphenol, and tributyltin chloride can promote T_H2 polarization (Kato et al., 2006), which may result in an increased development of atopic dermatitis-like lesions in DS-Nh mice after tributyltin exposure (Ohtaki et al., 2007). Additionally, there is evidence demonstrating that two estrogenic myco-toxins zearalenone and zearalenol can increase the expression of IL-5, a T_H2 cytokine, in the EL-4 thymoma cells (Marin et al., 1996).

(Xeno)estrogen and Food Allergy

The mucosal immune system is anatomically and functionally distinct from that found elsewhere in the body, e.g., the systemic immune responses. The mucosal immune system has developed specialized processes for antigen uptake,

transport, processing and presentation, the production of distinctive immune effector cells and molecules, and a specific homing mechanism (Kraehenbuhl, 1998). For example, the duodenal intraepithelial lymphocytes from infants are difficult to activate *in vitro* but exhibit markers of activation when compared with peripheral blood lymphocytes (Pérez-Machado et al., 2004). GI-associated lymphoid tissue can be divided into loosely organized effector sites, which include the *lamina propria* (LP) and intraepithelial lymphocytes, and more organized structures, such as mesenteric lymph nodes (MLNs), Peyer's patches (PP), isolated lymphoid follicles, and cryptopatches (CP) (Newberry and Lorenz, 2005). The PPs are secondary lymphoid tissues that are located along the wall of the small intestine, and they serve as the major sites for generation of immunity to intestinal antigens (Sato and Iwasaki, 2005).

Fed antigens are absorbed from the intestinal lumen either via the villus epithelium and specialized M cells of the intestinal epithelium or the mucosal LP and processed by underlying antigen-presenting cells, and passed to the organized lymphoid tissues of the PP and MLNs to sensitize the naïve T- and B-lymphocytes (Garside et al., 2004). It is believed that under normal circumstances, the gut immune system is relatively hyporesponsive to food antigens and commensal bacteria, and that this state of hyporesponsiveness (tolerance) is maintained by a number of important mechanisms including the integrity of gut epithelium and the presence of tolerogenic dendritic cells (DC) and T-regulatory (Treg) lymphocytes (Yang et al., 2007). Oral tolerance is a specific suppression of cellular and humoral immune responses to orally administered antigen upon subsequent immunization with the same antigen to prevent immune reactions to dietary antigens (Finamore et al., 2003). Thus, any perturbation to the homeostasis between gut antigens and the gut immune system may lead to gut inflammation and food allergy (Figure 1).

Significant actions for female sex steroids and xenoestrogens in the GI tract have been identified in various experimental models and clinical settings (Kawano et al., 2004). DES treatment

inhibited *Trichinella spiralis* expulsion and tissue reactions in the small intestine of adult mice by altering the immune responses that mediate expulsion of adult worms from the gut (Luebke et al., 1984). Estrogen-treated mice exhibited higher levels of *Candida albicans* colonization when compared to control mice; this was most evident in the small intestine and reproductive tract, which may be related to suppressed delayed-type hypersensitivity (DTH) responses (Hamad et al., 2002). Early studies in mice have shown that stimulation of the mononuclear phagocyte system by estrogen can prevent the oral ovalbumin (OVA)-induced systemic tolerance (Mowat and Parrot, 1983). After exposure of mice to DEP, the airborne particulates reached not only the lung but also the gut. Marked deposits of DEP in the mouse intestinal tissue following exposure suggest that DEP may act as a mucosal adjuvant in the gut and play a role in food allergy (Kadkhoda et al., 2004). Indeed, there is evidence that exposure to DEP can block induction of oral tolerance in mice (Yoshino et al., 1998, 2002; Yoshino and Sagai, 1999).

Additionally, benzo(a)pyrene has also been shown to enhance systemic T_H1 and T_H2 immune responses by acting as a mucosal adjuvant in the gut and may play a role in food allergy induction (Kadkhoda et al., 2004). In humans, food allergy prevalence is higher in boys before puberty, while this sex ratio is reversed after puberty (DunnGalvin et al., 2006). The data from a Norwegian national register of severe allergic reactions to food showed a strong dominance of reactions by females (60%) over males (40%); however, this sex difference was not apparent at 18 months of age (Lovik et al., 2003, 2004).

Nonetheless, there remains much to learn about the relationships between food allergies and (xeno)estrogen exposure. Why there are not clearer gender differences in the prevalence of food allergy if sex hormones and xenoestrogens are indeed playing a big role? The answer to this question is not known; however, it might be related to the time of exposure. The fetus, neonate, and child are often more sensitive than adults to environmental toxicants, especially estrogenic compounds (Aldridge et al., 2003). T-Lymphocytes in the cord blood of babies born to atopic mothers respond to aeroallergens as well as food allergens to which the mother was exposed during her pregnancy (Becklake and Kauffmann, 1999).

Neonates normally display a T_H2 cytokine bias in the gut (Scott et al., 2002), and at the same time, it seems that neonates of many species have more—and more potent—Tregs than adults, which may help explain why young animals show greater susceptibility to infections (Hartigan-O'Connor et al., 2007; Rouse and Sehrawat, 2007). If the neonatal immune system is not able to down-regulate the pre-existing T_H2 dominance effectively, an allergic phenotype may develop (Calder et al., 2006). It is possible that exposure to estrogen-like substances during the developmental stages may have contributed to the dramatic increase in the food allergy worldwide by shifting the immune development toward a T_H2 -biased state with less suppressor cell activity, which can be further exacerbated by estrogen exposure after puberty (Figure 2). Bisphenol A is recognized as a

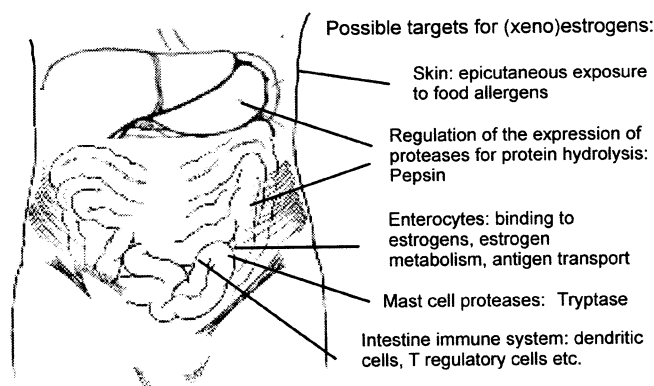


FIG. 1. Overview of possible (xeno)estrogen targets in relation to food allergy at the organ level.

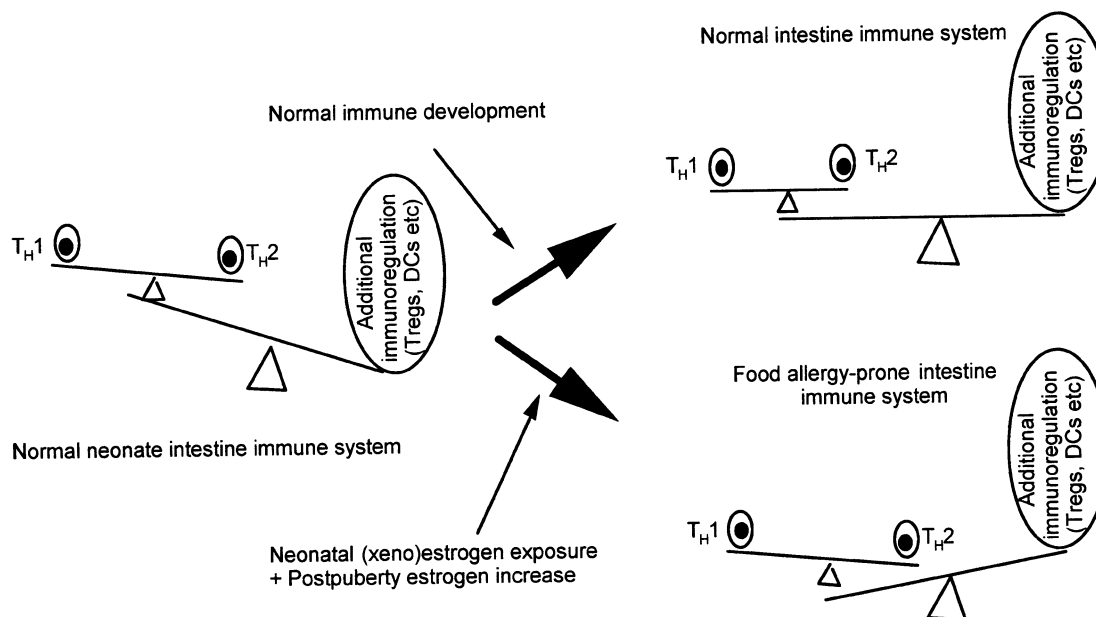


FIG. 2. The possible relationships between T_H1/T_H2 balance and additional immunoregulatory mechanisms during neonatal (xeno)estrogen exposure, and the presence of increased estrogens after puberty in females.

xenoestrogen due to its binding activity to estrogen receptors, and that it plays either estrogenic or anti-estrogenic roles *in vitro*. Ohshima et al. (2007) have shown that developmental exposure to bisphenol A interrupted the development of oral tolerance to food allergens in mice.

(Xeno)estrogen and Enterocytes

Enterocytes, the columnar epithelial cells in GI, are the major absorptive cells of the intestine, and they are born at the bottom of the crypts, pass through childhood migrating up the walls of the crypts, then settle down briefly to enjoy an absorptive adulthood on the villi. The differentiation of enterocytes is a dynamic process during which reinforcement of cell-cell adhesion favors migration along the crypt-to-villus axis (Schreider et al., 2002). The rapidity of enterocyte migration and maturation may provide a protective mechanism against carcinogenic toxins (Lin et al., 1999). The expression of ERs by epithelial cells of each segment of the rat intestine (duodenum, jejunum, ileum, and colon) has been reported (Thomas et al., 1993; Gejima et al., 2007).

In piglets, Chen et al. (2005) have shown that the mRNA expression of both $ER\alpha$ and $ER\beta$ can be detected in the small intestine. In addition, the GI mucosa has a high capacity for the metabolism of 17β -estradiol (E2) (Michnovicz and Rosenberg, 1992; Ruoff and Dziuk, 1994; English et al., 2000). Estrogen treatment can increase the expression of $ER\alpha$ in abomasum and $ER\beta$ in rectum (Pfaffl et al., 2003). These observations are important because these ER positive cells are the first to interact with the environmental estrogens uptaken orally. The phytoestrogen genistein (GEN), at the level present in soy infant for-

mula, is bioactive in the small intestine of piglets, and results in reduced enterocyte proliferation and migration (Chen et al., 2005); however, it has no effect in adult mice (Booth et al., 1999).

Recent epidemiological studies suggest that combined estrogen and progestogen hormone replacement therapy reduces the incidence of colorectal cancer (CRC) in post-menopausal women, and the protective effect against CRC seems to be through ERs (Konstantinopoulos et al., 2003; Wada-Hiraike et al., 2005). $ER\beta$ is the predominant ER expressed in colonic tissues. An $ER\beta$ -selective agonist has been reported to be an effective treatment in animal models of inflammatory bowel disease. These beneficial effects of estrogen treatment may be due to its modulatory effect on the immune responses (Harnish et al., 2004). However, the effect of estrogen on enterocytes and its contribution to the food allergic response in intestine is not known.

Normally, adult absorptive cells do not absorb macromolecules from the lumen, although neonatal absorptive cells are capable of endocytosing macromolecules from maternal milk, including immunoglobulins. Thus, the intestinal epithelium constitutes an efficient barrier to the penetration of massive amounts of food antigens. Additionally, the intestinal epithelium also regulates the antigenic information transmitted to the mucosal immune system. Transcytosis is a membrane traffic pathway of polarized cells in which ligand is internalized at one cell surface, sorted away from lysosomally directed ligands in the early sorting endosomes, and transported across the cell without entry into lysosomes (Burgess and Stanley, 1994). All proteins are absorbed across mucosal epithelia by transcellular transport and/or through interstitial spaces among the epithelial cells but not at equal levels (Matsuda et al., 2006).

However, the intestinal epithelial barrier function is abnormal in individuals with food allergies (Tu et al., 2005). In the first stage of food allergic response, food allergens are transferred intact across the epithelium into the LP mucosa of the digestive tract to initiate the interaction between food antigens and the mucosal immune system (Heyman and Desjeux, 2000; Fujita et al., 2007). The transepithelial antigen transport in sensitized rodents can be enhanced by binding of the antigen to IgE-CD23 (Fc ϵ R2) on the apical surface of epithelial cells, which is result from the secondary effect of an abnormal immunological response (Desjeux and Heyman, 1994; Bevilacqua et al., 2004; Tu and Perdue, 2006).

Ethinylestradiol can increase the transcytosis of asialofetuin and low-density lipoprotein (LDL) through mechanisms that alter the intracellular trafficking of the asialoglyco-protein receptor (Burgess and Stanley, 1994). In addition, estrogen causes intracellular diversion of LDL from the endocytic pathway, which would normally result in degradation in lysosomes, into a transcellular pathway resulting in the discharge of undegraded apo-lipoprotein B into the bile (Burgess and Stanley, 1997). Whether estrogen affects the food allergen transport across the intestinal epithelial barrier similarly is currently unknown.

(Xeno)estrogen and Proteases

The allergenicity of food proteins is dependent on their stability during digestion, e.g., resistance to digestive enzymes. One possibility that (xeno)estrogens affect the antigenicity of food allergens is by affecting the protein hydrolysis. Both partially and extensively hydrolyzed infant formulas have demonstrated a potential in protecting from allergic diseases such as atopic eczema and food allergy (Beyer, 2007; von Berg, 2007). Reduction in allergenicity and induction of oral tolerance of wheat gliadin by deamidation has been reported (Kumagai et al., 2007). Pepsin plays an important role in the digestion of peanut protein allergens, which is inhibited at high pH (Kopper et al., 2004). The stomach in infants shows a low amount of secretory pepsin (Yoshino et al., 2004). Importantly, gastrin-stimulated secretory rate of gastric H⁺ and pepsin were markedly inhibited in ovariectomized rat after 7 days of estradiol treatment (80 μ g/kg/day) in comparison to ovariectomized untreated rat and sham control (Piyachaturawat et al., 1983). In addition, tributyrin also significantly (20–50%) inhibited both fetal and postnatal aminopeptidase N (ApN) activity in the small intestine and colon (Kushak and Winter, 1999).

Trypsin, an abundant mast cell protease that is specifically released in large quantities from activated mast cells, can regulate mast cell activation and control allergic reaction by cleaving IgE to prevent it from binding to both allergens and Fc ϵ Rs (Rauter et al., 2008). The expression of trypsin in duodenal mucosa was decreased in children with food allergy (Augustin et al., 2001). Interestingly, estrogen can negatively regulate the uterine secretion of implantation serine proteinase (ISP) 1 and 2 at the post-transcriptional level. The ISP1 gene may encode the embryo-

derived enzyme strypsin, while the ISP2 gene encodes a related tryptase, which is expressed in endometrial glands (O'Sullivan et al., 2004).

(Xeno)estrogen and Dendritic Cells (DC) in GI Tract

Dendritic cells are recognized for their ability to internalize antigens at an extremely low concentration and for their highly efficient presentation of these antigens in the context of the major histocompatibility complex (MHC) Class II molecules to naive T-lymphocytes. The DC are believed to play an essential role in regulating the balance between immunogenic and tolerogenic responses to mucosal antigens by controlling T-lymphocyte differentiation and activation via cytokine co-stimulatory and co-inhibitory signals (Neurath et al., 2002). The intestine and its lymphoid organs contain large number of DC (including a number of unique subsets), and expansion of DC in mice using the cytokine flt3 ligand (flt3L) or enhancement of their survival with the TNFR family member RANK-ligand (up-regulate IL-10 in mucosal DC and IL-12 in splenic DC) markedly increased the induction of oral tolerance in these mice (Bilsborough and Viney, 2004; Fleeton et al., 2004).

The incoming antigens are sampled by the DC that resides just under the subepithelial dome region. This local sampling of antigens by DC in the PP is critical for the induction of adaptive mucosal immunity (Sato and Iwasaki, 2005). In contrast to splenic DC that induces CD4⁺ T-lymphocyte proliferation, it is possible that intestinal DC induce minimal T-lymphocyte proliferation or even suppress CD4⁺ T-lymphocyte proliferation. The phenotype of intestinal DC is not fixed, and can be modulated by adjuvants or inflammatory cytokines and, possibly, (xeno)estrogens. There is evidence that neonatal DCs are intrinsically biased against Th-1 immune responses (Langrish et al., 2002). However, other reports suggest that neonatal DCs are fully competent in their innate immune functions (Sun et al., 2003), and their MHC class I antigen processing and presentation pathway is also functional (Gold et al., 2007).

The endocrine system regulates the maturation of different DC subtypes. The expression of ER α and ER β by DC at all stages of differentiation has been reported (Salem et al., 2000; Sapino et al., 2003; Mao et al., 2005). The ER antagonists ICI 182,780 and tamoxifen can block the differentiation of the E2-responsive DC population (Paharkova-Vatchkova et al., 2004). E2 can enhance DC antigen-presenting function *in vivo* in the absence of inflammation and thus promote autoimmunity (Paharkova-Vatchkova et al., 2004), possibly by enhancing the T-lymphocyte stimulatory capacity of mature DC since estrogen-exposed DC express higher levels of MHC class II and co-stimulatory molecules (Pettersson et al., 2004). Other potentiating effects of estrogen include: E2 enhances the secretion of IL-6 in immature DC (iDC); E2 modulates the production of the DC-derived chemokines IL-8, MCP-1, MDC, and TARC; E2 provides a signal essential for migration of mature DC toward CCL19/MIP3b (Bengtsson et al., 2004).

The endocytosis is an important property of immature DC. During the process of the maturation, DC appear high stimulatory capacity and low endocytosis, and E2 decreases the endocytosis of DC (Yang et al., 2006). On the other hand, estrogen treatment did not alter the function of mouse plasmacytoid DC that were derived from estrogen-resistant myeloid progenitors (Harman et al., 2006). In experimental autoimmune encephalomyelitis, systemic E2 treatment led to decreased numbers of DC migrating into the central nervous system at disease onset, and decreased DC production of tumor necrosis factor (TNF)- α , IL-12, and interferon (IFN)- γ (Liu et al., 2002). Taken together, a consistent pattern of estrogen effects on DCs does not emerge from studies reported so far, possibly due to the heterogeneity. Nonetheless, it suggests that the function of DC, including those residing in the GI, can be affected by estrogen.

(Xeno)estrogen and Tregs in GI Tract

The gut is home to a large number of Tregs, and several types of Tregs have been induced after a repeated feeding of a low dose of antigen. These include TGF- β -producing T_H3 cells (Pérez-Machado et al., 2003), IL-10-producing Tr1 cells (Battaglia et al., 2004), and CD4⁺CD25⁺Foxp3⁺ T-lymphocytes (Sun et al., 2007), Natural killer T (NKT) cells (Rocha-Campos et al., 2006), CD8⁺ T suppressor lymphocytes and TCR $\gamma\delta$ T-lymphocytes (Mengel et al., 1995; Ke et al., 1997). Large amount of evidence suggests for cross talk between these Tregs (Chen et al., 2003; Chung et al., 2005; Battaglia et al., 2006; Ly et al., 2006; DiPaolo et al., 2007; Wu et al., 2007). Furthermore, as mentioned above, the immune system of neonates is empowered with a tremendous regulatory potential, which can be developed independently of thymus (Dujardin et al., 2004).

A subset of well-characterized Tregs is the CD4⁺CD25⁺Foxp3⁺ T-lymphocytes. Based on their origin, two types of CD4⁺ Tregs have been described, e.g., naturally occurring Tregs (nTregs) that originate and mature in the thymus, and inducible (or adaptive) Tregs (iTregs). The iTregs develop extra-thymically from conventional CD4⁺ T-lymphocytes that are activated under conditions of impaired co-stimulatory signaling or are induced by suppressive cytokines and drugs (De Luca et al., 2007). Both experimental animal and human studies have convincingly demonstrated that CD4⁺CD25⁺ Tregs are crucial in the regulation of food allergy (Karlsson et al., 2004; Herberth et al., 2006; Torgerson et al., 2007; van Wijk et al., 2007; Yang et al., 2007).

Oral exposure to protein induces activation of functional CD4⁺CD25⁺ T-lymphocytes in the gut-draining lymph nodes in mouse models (Torgerson et al., 2007). The studies from van Wijk et al. (2007) have suggested that the induction of oral tolerance to peanut extract (PE) is impaired in CD4⁺CD25⁺ T-lymphocyte-depleted animals; in sensitized mice, the depletion of CD4⁺CD25⁺ T-lymphocytes results in increased allergic responses to PE.

These studies suggest that CD4⁺CD25⁺ T-lymphocytes play an important role in both controlling tolerance induction and

regulating the intensity of allergic responses to peanut. Patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, or X-linked autoimmunity-allergic dysregulation syndrome lack CD4⁺CD25⁺ Tregs because of a Foxp3 mutation, and they often develop food allergic reactions and increase specific IgE antibody levels accompanied by severe eczema (Herberth et al., 2006). Children, who have outgrown their cow's milk allergy and developed tolerance, have a higher percentage of CD4⁺CD25⁺ T-lymphocytes with regulatory function in the peripheral blood than allergic children (Karlsson et al., 2004; Torgerson et al., 2007).

Although some evidences suggest that estrogen treatment in adult animals at levels equal or higher than that found during pregnancy expands the compartment of CD4⁺CD25⁺ Tregs (Polanczyk et al., 2004, 2006; Tai et al., 2008), the role estrogen at lower levels on CD4⁺CD25⁺ Tregs is not known, and not even a mention of its developmental effect in mucosal tissue. This is important considering the biphasic effect of estrogen on the immune response, as discussed earlier. However, it should be noted that prenatal exposure to bisphenol A has been shown to augment both T_H1 and T_H2 responses at least partially by decreasing CD4⁺CD25⁺ Tregs in adult mice (Ohshima et al., 2007). Similarly, developmental exposure to genistein also decreased CD4⁺CD25⁺ T-lymphocytes in adult female mice (discussed next).

NKT cells are increasingly recognized as important immunoregulatory cells. They are defined as expressing both natural killer 1 (a member of the natural killer cell receptor family, NKR-P1, CD161) and CD3 surface markers (Grose et al., 2007). CD1d represents a restriction element for invariant NKT (iNKT) cells. The role of CD1d in the regulation of intestinal immune responses was first suggested by experiments showing that a mixed lymphocyte reaction between intestinal epithelial cells and CD8⁺ T-lymphocytes was inhibited by a mAb against CD1.

Large amounts of CD1d positive cells have been found in the LP of patients with cow's milk hypersensitivity both at the time of GI manifestations and during asymptomatic periods when compared to healthy individuals who did not show any CD1d expression in the duodenum. The localization of CD1d positive cells corresponded to areas where B-lymphocytes, plasma cells, and DC were present (Ulanova et al., 2000). The iNKT cells are also detected in the duodenum of healthy individuals using α -galactosylceramide loaded CD1d tetramers; however, they are deficient in subjects with coeliac disease (Grose et al., 2007).

iNKT cells can function to skew adaptive immunity toward T_H2 responses (Meyer et al., 2007). CD4⁺ iNKT cells are thought to be the major source of T_H2 cytokines (Sakuishi et al., 2007); IL-4 and IL-13 secreted by iNKT cells has been highlighted in the pathogenesis of asthma (Akbari et al., 2003; Meyer et al., 2006). However, negative regulation of T_H2-responses by the activated NKT has also been reported (Iwamura and Nakayama, 2007). Neonatal NKT cells differ from their adult counterparts: they express markers of activation, such as CD25; they are polyclonal; and they do not produce cytokines in

response to primary stimulation (D'Andrea et al., 2000). Limited information is currently available for estrogen's effect on iNKT cells. Gourdy et al. (2005) have shown that adult estrogen treatment increased IFN γ production by peripheral iNKT cells. However, the effect of (xeno)estrogen exposure during various period of life on the mucosal NKT cells is unknown.

Other Routes of (Xeno)estrogen Exposure

We have presented above possible targets of (xeno)estrogen in modulating food allergy as a result of oral/dietary exposure to food proteins. However, there is increasing evidence that sensitization to food allergens can be acquired via other routes. It became evident that some children had allergic reactions following their apparent first ingestion of peanuts. IgE-mediated food allergy has co-morbid conditions, such as atopic dermatitis and asthma. Impaired function of the epidermal skin barrier is characteristic of atopic dermatitis, and sensitization to allergens through the skin is a possibility.

A cohort study has shown that the use of peanut-containing creams was more common in children who subsequently became allergic to peanut than in control infants, suggesting that some sensitization to peanut may have occurred through the skin (Lack et al., 2003). In animal models, Strid et al. (2005) have shown that epicutaneous exposure to peanut protein prevents oral tolerance induction. In addition, exposure to antigens from the mother's skin is one of the key events that promote maturation of the infant's gut and gut-associated immune systems (Calder et al., 2006). There is likely to be occupational and residential exposure to (xeno)estrogens, and thus, examination of interaction between food allergen and (xeno)estrogens following dermal exposure will not only shed light on the effect of routes of exposure on food allergy induction but also the role of (xeno)estrogens in this complex disease.

Genistein, Windows of Exposure, T_H1-T_H2 Polarization and Food Allergy

Genistein, a major isoflavone in most soy products, is consumed in supraphysiologic levels as nutritional supplements and pharmaceuticals (Li et al., 2003). GEN has a 2-phenyl-naphthalene-type chemical structure sharing several features in common with that of E2, including a pair of hydroxyl groups separated by a similar distance, and has been demonstrated to interact with estrogen receptors *in vivo* (Martin et al., 1978). GEN exhibits weak estrogenic activity on the order of 10^{-2} to 10^{-3} compared to that of E2 (Miksicek, 1994), but it is present in the body in concentrations much higher than those of endogenous estrogens (Adlercreutz et al., 1993). GEN has higher affinity to ER β than to ER α . Infants fed soy milk formulas have plasma isoflavone levels that are orders of magnitude higher than those of infants fed human or cows' milk (Setchell et al., 1997). Despite the hypothesized beneficial effects of GEN (e.g., decreased incidences of some hormone-related cancers), there are concerns about the potential long-term effects of this com-

pound on human health, especially that of infants and young children.

A retrospective multiple controlled cohort study has indicated that there was an increase in the use of allergy drugs in young adults (with statistically significant changes in females) who had been fed soy formula during infancy as compared to those who were fed cow milk formula from the age of less than 9 days old when both groups were healthy-term infants whose mothers elected not to breastfeed (Strom et al., 2001).

Furthermore, soy frequently causes food allergy especially in childhood (Christensen et al., 2004). In a study conducted in Sweden, consumption of soy was thought to be responsible for several fatal food anaphylaxis in children and young adults either by itself or by synergizing with peanut (Foucard et al., 1999). Phytoestrogens have also been detected in amniotic fluid (Doerge et al., 2001), suggesting that *in utero* exposure also occurs. Furthermore, the metabolic and/or excretion rates of GEN are different between mother and fetus, and once GEN is transferred to the fetus, it tends to stay in the fetus longer than in the mother (Todaka et al., 2005).

As reviewed above, estrogen can decrease cell-mediated immunity in mice (Holmdahl and Jansson 1988; Salem et al., 2000) and in women (Hoek et al., 1995). It has been suggested that the mechanism of the suppression is through ERs on the target cells. Because of the similarities of GEN to estrogen, and its affinity to ERs, studies have been done to see if GEN has immunosuppressive effects. Yellayi et al. (2002) have shown that subcutaneous injections of GEN not only suppressed humoral immunity but also decreased thymic weight and produced thymic atrophy; however, the dose of GEN was high and route of exposure was physiologically irrelevant (Cooke et al., 2006). Similar shortcomings existed in studies by Verdrengh et al. (2003), who have shown that subcutaneous injection of GEN-suppressed DTH reactions.

We have investigated the effects of developmental GEN exposure on serum total IgE production, following dermal exposure to the allergen trimellitic anhydride (TMA) in B₆C₃F₁ mice using a physiologically relevant exposure route, e.g., oral exposure. Increased serum total IgE production while decreased IgG_{2a} and IgG_{2b} production was observed in the *in utero* GEN-exposed adult female B₆C₃F₁ mice (Guo et al., 2005). Furthermore, increased IgE production in these mice was associated with a decrease in the percentage of CD4⁺CD25⁺ T-lymphocytes, and increases in the production of cytokines (IL-2 and IL-4), expression of B7.2 by B-lymphocytes and activity of eosinophil peroxidases. In our study with younger female mice, e.g., at postnatal day (PND) 38, *in utero* exposure to GEN did not affect the total serum IgE production in response to TMA, suggesting that sexual maturation was necessary to manifest an enhanced IgE production (Guo et al., 2005; data not shown).

The exact mechanism underlying the developmental basis of the adult disease is currently unclear. In contrast, an enhancement in T_H1 immune response was observed in our studies with

GEN exposure in adult B₆C₃F₁ mice. Our studies have demonstrated that exposure of adult female B₆C₃F₁ mice to GEN by gavage at doses of 2–20 mg/kg increased the activities of cytotoxic T-lymphocytes (CTLs) in both *ex vivo* (Guo et al., 2001) and *in vivo* systems (Guo et al., 2007). Moreover, increased activities of CTLs correlated with an increase in the production of IFN γ and activation of signal transducers and activators of transcription (STAT) 1 and STAT4.

These results are confirmed indirectly by Kogiso et al. (2006) who showed that OVA-specific T_H2-antibody IgG₁ production was decreased following GEN exposure in adult mice. The fact that GEN exposure in adults enhances cell-mediated immunity agrees with epidemiological studies that there is a negative correlation between GEN intake and allergic reactions. There are reports that GEN exposure in adult may provide some protection against asthma (Smith et al., 2004) and reduce the incidence of chronic respiratory symptoms (Butler et al., 2004; Miyake et al., 2005). Therefore, exposure to GEN may modulate T_H1/T_H2 balance depending on the window of exposure (*in utero* versus adult exposure).

CONCLUSION

There are sufficient evidences to make us believe (xeno)estrogens can regulate the development of food allergy. These (xeno)estrogens may exert their effects on the enterocytes, proteases involved in protein digestion and allergy regulation, intestinal DC and Tregs through binding to ERs directly or through interfering the binding of endogenous estrogens to the ERs. Early developmental periods may be particularly sensitive. More research (both clinical and animal studies) using specific immunomodulatory compounds (e.g., GEN) interfering with immunoregulatory mechanisms (e.g., the T_H1/T_H2 balance) may help us obtain information that we are currently lacking, including gender and sex differences on food allergy.

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