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Placental immune response to apple allergen in allergic mothers

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ABSTRACT

The immunological milieu in the placenta may be crucial for priming the developing foetal immune system. Early imbalances may promote the establishment of immune-mediated diseases in later life, including allergies. The initial exposure to allergens seems to occur in utero, but little is known about allergen-induced placental cytokine and chemokine release. The release of several cytokines and chemokines from placenta tissue after exposure to mast cell degranulator compound 48/80 or apple allergen in placentas from allergic and healthy mothers was to be analysed. Four placentas from women with apple allergy and three controls were applied in a placental perfusion model with two separate cotyledons simultaneously perfused with and without apple allergen (Mal d 1). Two control placentas were perfused with compound 48/80. In outflow, histamine was quantified spectrophotofluorometrically, IL-2, IL-4, IL-6, IL-10, TNF and IFN-γ by a cytometric multiplex bead array and IL-13 and CXCL10, CXCL11, CCL17 and CCL22 with an in-house multiplex Luminex assay. Compound 48/80 induced a rapid release of histamine, CXCL10, CXCL11, CCL17 and CCL22, but not of the other factors. Apple allergen induced a time-dependent release of IL-6 and TNF, but not of histamine, in placentas of women with apple allergy compared with the unstimulated cotyledon. CCL17 levels were slightly increased after allergen stimulation in control placentas. Allergens can induce placental cytokines and chemokines distinctly in allergic and healthy mothers. These mediators may affect the prenatal development of the immune system and modify the risk of diseases related to immune disorders in childhood such as allergies.

1. Introduction

The prevalence of allergic diseases has increased during the last few decades (Burr et al., 1989; Asher et al., 2006). Genetic factors are important for allergy development, but a time period of 30–40 years is considered to be too short for human genetic composition to undergo such dramatic changes causing this increasing prevalence. As a

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consequence, a lot of attention has been drawn to the postnatal exposure to environmental factors associated with a westernised lifestyle. Exposure to environmental factors important for allergy development appears to be important very early in life, perhaps even before birth (Jenmalm and Bjorksten, 1998). This concept was first developed in 1989, when D.J.P. Barker highlighted the possible link between events in utero and the development of diseases in adult life, called "foetal programming of diseases" (Barker et al., 1989). Prenatal farm exposure reduces the risk of asthma symptoms, allergic rhinoconjunctivitis and eczema (Douwes et al., 2008) and maternal exposure to stables during pregnancy protects against allergic sensitisation, whereas exposure later in life has limited or no effect at all (Ege et al., 2006; Lampi et al., 2011). However, the role of the gestational environment in shaping immune responses in the offspring and in the development of allergic diseases needs further investigation.

The initial exposure to allergens may occur in utero. House dust mite allergen has been detected in the amniotic fluid and in the foetal circulation, indicating a transamniotic and a transplacental transfer (Holloway et al., 2000). Dual perfusion experiments have shown a maternal–foetal passage of β-lactoglobulin, ovalbumin and birch pollen (Loibichler et al., 2002; Edelbauer et al., 2003, 2004) but also an accumulation of allergen in the syncytiotrophoblast cell layer (Szepfalusi et al., 2006). Detectable allergen-specific T cell responses at birth, shown as the capability of cord blood mononuclear cells (CBMC:s) to produce cytokines in response to allergens, support the idea of intrauterine allergen exposure and the priming of the foetal immune system (Kondo et al., 1998; Van Der Velden et al., 2001). On the other hand, the neonatal CD4+ T cell population has shown a typical phenotype of recent thymic emigrants, with receptors lacking the specificity of conventional T cells, and may thus be capable of interacting with a multitude of antigens, i.e. allergens (Thornton et al., 2004).

Human term placenta consists of several cell populations including fibroblasts, smooth muscle cells, endothelial cells, cyto- and syncytiotrophoblast cells and immune cells such as macrophages, T cells and mast cells. Many of these cells are able to produce cytokines and chemokines, but macrophages, endothelial cells and trophoblast cells can account for most of the production (Steinborn et al., 1998; Keelan et al., 1999). The chemokines function as attractants for leukocytes to the site of inflammation and the regulation of leucocyte maturation (Pease and Williams, 2006). The interleukin (IL)-4- and IL-13-induced chemokines CCL17 and CCL22 (Andrew et al., 1998; Nomura et al., 2002) bind to the CCR4 receptor expressed on Th2 lymphocytes, mast cells, dendritic cells and natural killer T (NKT) lymphocytes (Pease and Williams, 2006). The interferon-γ (IFN-γ)-induced chemokines CXCL10 and CXCL11 (Luster and Ravetch, 1987; Cole et al., 1998) attract CXCR3 receptor-expressing Th1 lymphocytes, NKT and mast cells (Pease and Williams, 2006).

Although allergy is associated with increased allergen-induced levels of IL-4, IL-5, IL-13, CCL17 and CCL22 by peripheral mononuclear cells (PBMCs) (Imada et al., 1995; Till et al., 1997a,b; Sun et al., 2007), little is known about the allergen-induced cytokine and chemokine production at the local level in the placenta. Furthermore, allergen-induced mast cell degranulation in the placenta has not been demonstrated. A pronounced placental Th2 shift in allergic mothers has been suggested to explain the greater risk of maternal allergy compared with paternal allergy for the development of allergic diseases in the offspring (Ruiz et al., 1992; Liu et al., 2003). Furthermore, the higher cord blood (CB) IgE levels in children of allergic mothers than in children with paternal or no allergic history (Johnson et al., 1996; Liu et al., 2003) support a possible exaggerated placental Th2 phenotype among the allergic women. Exposure to a strong Th2 milieu during foetal development could generate long-lasting effects in the offspring by modulation of their immune responses, to an IgE favouring, Th2-like phenotype, possibly promoting allergy development later in life.

The aim of the present study was to analyse the cytokines IL-2, IL-4, IL-6, IL-10, IL-13, IFN-γ, tumour necrosis factor (TNF), the chemokines CXCL10, CXCL11, CCL17, CCL22 and histamine release in placentas after stimulation with apple allergen or the mast cell degranulating compound 48/80 in relation to maternal allergic disease.

2. Materials and methods

2.1. Subjects

Four women with an oral allergy syndrome displaying allergic symptoms to apple and 5 women without any allergic symptoms from the Jena area, region of Thuringia, Germany, were included in the study. The following inclusion criteria were applied: delivery after week 37 of pregnancy, a healthy, appropriately grown newborn, an absence of maternal chronic metabolic diseases, pharmacological therapy and pregnancy complications. In their anamneses, none of the allergic patients had reported systemic reactions, but only the classical local reactions as described for the oral allergy syndrome (Ortolani et al., 1988). The similar severity of the symptoms described did not allow subdivision of the patient group. All study participants gave their written informed consent. The regional ethics committee of the Medical Faculty of Friedrich Schiller University Jena approved the study (No. 1038-02/03).

In advance of delivery, circulating allergen-specific IgE antibodies to the major allergens of apple (Mal d 1) and birch (Bet v1; because of their cross-reactivity (Klinglmayr et al., 2009)) were measured in serum of the allergic women by using specific IgE tests (ImmunoCAP; Phadia, Freiburg, Germany) and a Phadia®250 system. If this was not practicable, a rapid immunographic allergy screening test (Auro Dex Visual-ENS test, including birch, other tree and grass pollen, and frequent animal allergens; Dexall, Gaithersburg, MD, USA) was conducted in the delivery room. After delivery, results were confirmed by an ImmunoCAP test. Sensitisation to additional allergens did not lead to exclusion. Both of the rapid diagnosis allergy tests were also used to exclude allergic sensitisation in the anamnestically non-allergic women. The sensitivity and specificity of the Auro-Dex Visual-Ens has been assessed previously (Pietsch, 2006).