Expression of CD21 and CD23 during Human Fetal Development

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ABSTRACT

Neonates produce lower levels of IgE compared with adults. Diminished IL-4 production and impaired up-regulation of CD40L by neonatal T cells could explain this, however other regulators of IgE production, such as CD21 and CD23, could contribute to reduced circulating IgE levels during fetal development. Heparinized blood samples were collected from adults and from the umbilical cord at premature and term births. Whole blood flow cytometry was used to assess the percentage of T (CD3$^+$) and B (CD19$^+$) lymphocytes expressing CD21 and/or CD23 at 26–29 ($n = 3$), 30–33 ($n = 7$), 34–37 ($n = 5$), and >37 ($n = 11$) wk of gestation, as well as in adults ($n = 15$). Plasma-soluble CD21 was also measured. At term, the percentage of CD21$^+$ and CD23$^+$ B cells was comparable to the adult, however, the percentage of cells positive for each of these surface antigens was decreased significantly before term. The percentage of T cells expressing CD21 from all gestations was significantly higher than the adult and the percentage positive decreased with increasing gestational age. Conversely, soluble CD21 levels increased with increasing gestation to be comparable to the adult by term. Thus, it is unlikely that altered expression of CD21 and CD23 on B cells contributes to the low level of IgE in the neonatal circulation unless functional differences occur or a lack of processing to the soluble form is important in regulating IgE production. However the abundance of CD21-positive T cells could alter the T- and B-cell interaction necessary for IgE switching by B cells and, thereby, especially with impaired IL-4 production, limit IgE production. (*Pediatr Res* **52: 245–250, 2002**)

Abbreviations
sCD21, soluble CD21
sCD23, soluble CD23
CD40L, CD40 ligand (CD154)

Isotype switching to IgE production by human B cells requires a well-coordinated series of events. Thus IL-4 (and to a lesser extent IL-13) and the cognate interaction of B cell (CD40) with T cell (CD40L, CD154) have now been identified as the minimal requirements for the transcription of germline epsilon message and secretion of IgE (1, 2). IgE levels in the circulation of neonates born in Westernized countries are characteristically very low, ranging from not detectable to <2 IU/mL (3, 4). Nevertheless, as IgE does not traverse the placenta (5, 6), IgE in the fetal circulation probably represents fetal production, although, as IgE is detectable in amniotic fluid where it might be of maternal origin (7), any IgE detected in the fetal circulation could reflect IgE of both fetal and maternal origin. IgE production by fetal tissues has been demonstrated to occur in the fetal liver and lung from as early as 11 wk of gestation, and by 21 wk of gestation explants of fetal spleen can also synthesize IgE (8). Active transcription of sterile Iϵ occurs in the liver, spleen mesentery and gut as early as 8 wk of gestation but VDJCϵ transcripts cannot be detected until 18 wk of gestation (in two of 18 fetal liver samples) (9) and circulating IgE cannot be detected until 25 wk of gestation (Jones *et al.*, submitted). As total IgE levels can be very high in neonates born in countries where parasitosis still occurs (10), the neonate is obviously not impervious to production of adult equivalent levels. Furthermore, the ability to detect allergen- and parasite-specific IgE at birth (10, 11) implies that isotype switching of B cells in response to antigen can occur during fetal life. However, very little is known about the regulation of IgE production by the fetus and neonate.

The lower production of IgE by neonatal B cells has catalyzed numerous analyses of B- and T-cell phenotype. Neonatal B-cell expression of CD40 is similar to the adult (12), and responses to CD40 stimulation can be induced (13, 14). Expression of CD40 ligand (CD40L, CD154) is variably described as reduced or comparable to the adult, depending upon the stimulation used (12, 13, 15–19). In contrast, IL-4 production by umbilical cord blood mononuclear cells is consistently described as lower than that from adult peripheral blood mononuclear cells, irrespective of the stimulus used (14, 20). The lack of IL-4 and/or CD40 ligand may be the limiting factor in

IgE production by the neonate, as a number of investigators have found that exogenous IL-4 in conjunction with CD40 cross-linking increased IgE production by umbilical cord blood mononuclear cells (13, 14, 16, 17).

The interaction of CD23 and CD21 has also been shown to have an important role in IgE production and is considered to control IgE production in a more isotype-specific fashion (2). Therefore, altered expression or function of other IgE regulatory molecules such as the ligand pair CD23 and CD21 could also contribute to the poor production of IgE by Western neonates. CD23 is a 45-kD type II membrane glycoprotein that in humans occurs as two different isoforms, a (constitutively expressed on B cells) and b (up-regulated on B and other hematopoietic stimuli such as IL-4), and serves as the low-affinity IgE receptor. Membrane CD23 has a role in down-regulation of IgE production (21, 22). CD21 is a 140-kD membrane glycoprotein predominantly expressed by B lymphocytes and follicular dendritic cells and is a receptor for CD23. The occupancy of CD21 on B cells enhances IgE production (23). The CD21/CD23 ligand pair is poorly studied in the neonate, therefore, we undertook an investigation of the developmental regulation of CD21 and CD23 pair during the third trimester of pregnancy.

MATERIALS AND METHODS

Samples. Fetal blood was collected by umbilical vein or cardiac puncture from fetuses delivered for medical reasons using prostin with informed consent from the mother. Blood was also collected by umbilical vein puncture from neonates delivered at term and prematurely and by venepuncture from healthy adult controls with informed consent where appropriate. All bloods were collected into lithium heparin (Vacutainer, BD Biosciences, Franklin Lakes, NJ, U.S.A.) and samples were processed within 3 h of collection. None of the premature infants were known to have abnormalities of the immune system at birth. Whole blood was used for flow cytometry as described below and plasma was obtained after density gradient centrifugation of undiluted blood on Histopaque (Sigma Chemical, Poole, Dorset, U.K.) (cells were used for other studies). Plasma was filtered, aliquoted, and stored at $-80°C$ until analysis. The study was approved by the Southampton and S.W. Hants Joint Research Ethics Committee and fulfilled the requirements of the Polkinghorne Committee report on the research use of fetuses and fetal tissues.

Flow cytometry. Whole blood (50 μL) was placed in a fluorescence-activated cell sorter (FACS) tube with a preoptimized concentration of fluorochrome-conjugated antibodies and incubated in the dark and on ice for 30 min. Red blood cell lysis was conducted by the addition of 2 mL of $1\times$ FACS Lysing Solution (BD Biosciences) and incubation at room temperature for 12 min. After centrifugation at $400 \times g$ at 4°C for 7 min, the pellet was washed twice by centrifugation with 3 mL PBS/0.5% BSA/0.2% sodium azide. The pellet was resuspended in 100 μL of 1% paraformaldehyde and stored in the dark at 4°C until acquisition by flow cytometry (FACScan, BD Biosciences) within 2 d of staining. The population identified by characteristic side scatter and CD3 or CD19-positivity

was acquired (5,000–10,000 events, with total events collected and saved) for analysis using CellQuest software (BD Biosciences). The following antibodies (Ancell, Alexis Corporation, Nottingham, U.K.) were used for this study: anti-CD19 conjugated to FITC (mIgG1, clone BU12), anti-CD3 conjugated to FITC (mIgG1, clone UCHT1), anti-CD23 conjugated to R-phycoerythrin (mIgG1, clone BU38), and anti-CD21 conjugated to R-phycoerythrin (mIgG1, clone BU33). An isotype control was included as appropriate (mIgG1, clone MOPC-21, BD PharMingen, San Diego, CA, U.S.A.).

ELISA. Plasma sCD21 levels were measured with a specific ELISA (Diatec, IDS Ltd, Tyne and Wear, U.K.) according to the manufacturer's instructions. All samples were assayed after a 1:2 dilution in the sample buffer provided with the kit and the sensitivity of the assay was 3 U/mL.

Statistical analysis. The percentage of $CD23^+$ or $CD21^+$ cells (B or T) in each group was compared using Mann Whitney U test and the maturation of sCD21 was assessed using Kruskall-Wallis (SPSS, Version 8.0, SPSS Inc., Chicago, IL, U.S.A.; StatView, Version 5.0, SAS, Cary, NC, U.S.A.).

RESULTS

Expression of CD23 and CD21 on $CD19^+$ B cells. B cells were identified by their characteristic side-scatter profile and CD19 positivity (Fig. 1a). After setting a gate on this population (R1), 3000–5000 events within the gate were acquired and analyzed. Examples of results for CD21 expression (Fig. 1c) and CD23 expression (Fig. 1d) as well as the isotype control (Fig. 1b) are shown for both adult peripheral and for umbilical cord blood. At term (>37 wk of gestation, $n = 11$), the percentage of B cells expressing CD23 was comparable to the adult ($n = 13$, Fig. 2a), with the percentage of $CD23^+$ B cells at earlier gestational ages reduced in comparison to the levels at term and in the adult. Statistically significant differences were observed for the differences between adults and 26–29 ($n = 3$, $p = 0.039$) and 30–33 ($n = 7$; $p = 0.03$) wk of gestation, and only for 30–33 wk of gestation compared with the term neonate ($p = 0.02$) (Fig. 2a). Similarly, the percentage of $CD21^+$ B cells was comparable in the adult ($n = 15$) and term ($n = 11$) neonate and significantly lower at 26–29 ($n = 3$, $p = 0.005$), 30–33 ($n = 6$, $p = 0.003$), and 34–37 ($n = 4$, $p = 0.027$) wk of gestation compared with the term neonate, and at 26–29 ($p = 0.027$) and 30–33 ($p = 0.036$) wk the percentage of $CD21^+$ B cells was significantly reduced in comparison to adults (Fig. 2b).

Expression of CD21 on T lymphocytes. T cells were identified by their characteristic side scatter and CD3 expression (Fig. 3a). Events (10,000) within the gate (R1) were acquired and analyzed. Examples of the results obtained for adult and umbilical cord blood for both the isotype control (Fig. 3b) and CD21 (Fig. 3c) are shown. In contrast to adult $CD3^+$ cells that were virtually devoid of membrane CD21 expression, umbilical cord blood $CD3^+$ cells had a distinct subpopulation of $CD21^+$ cells. The percentage of $CD3^+$ cells expressing CD21 decreased with increasing gestational age but remained significantly higher than adult levels at all gestational time points examined [26–29 wk ($n = 3$), $p = 0.012$; 30–33 wk ($n = 5$),
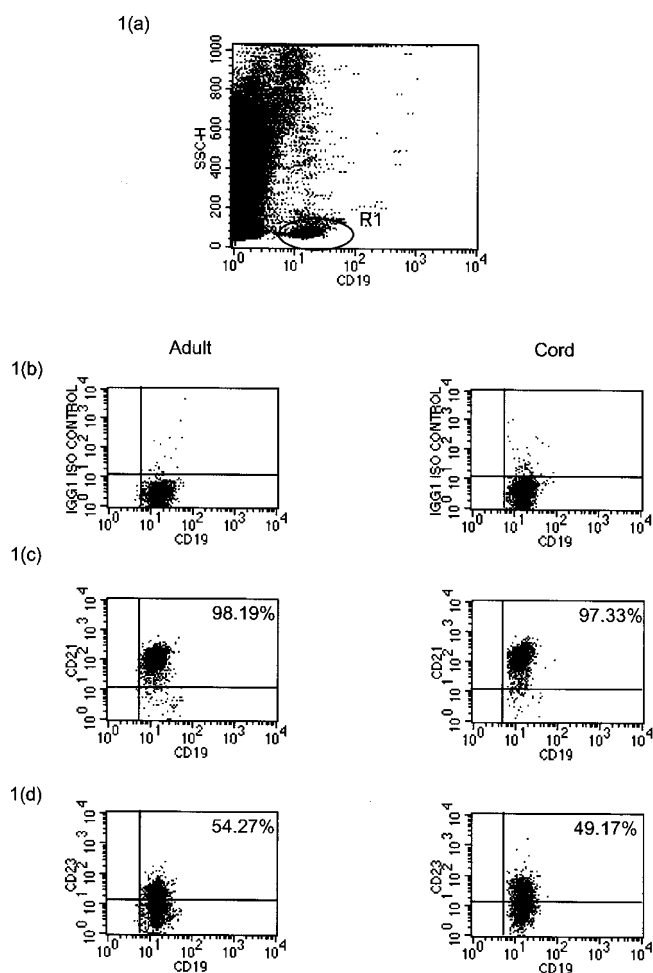
1(a)

Adult   Cord

1(b)

1(c)

98.19%   97.33%

1(d)

54.27%   49.17%

Figure 1. The identification of B cells expressing CD23 and CD21. B cells were (*a*) identified by their characteristic side-scatter profile and CD19 positivity, and then 3000–5000 events (*R1*) were analyzed with phycoerythrin-conjugated (*b*) isotype control (mIgG1), (*c*) anti-CD21, or (*d*) anti-CD23 control. Examples of results obtained with umbilical cord and adult blood are shown.

Figure 2. The percentage of B cells expressing CD23 and CD21 over gestation. Flow cytometry was used to determine the percentage of B cells from fetuses/neonates of different gestations and adults expressing (*a*) CD23 and (*b*) CD21. *Significant difference ($p < 0.05$) compared with the adult; **significant difference compared with term.

$p = 0.002$; 34–37 wk ($n = 4$), $p = 0.016$; >37 wk ($n = 6$), $p = 0.001$ compared with adults ($n = 8$)]. At the earliest time points examined in this study, 26–29 and 30–33 wk, 28.9% and 28.2%, respectively, of the CD3$^+$ cells expressed CD21, and by 34–37 wk and term (>37 wk of gestation) this had decreased to 16.2% and 19.4%, respectively, of the CD3$^+$ cells. There was no significant difference between the fetal/neonatal samples at different gestational ages (Fig. 4*a*). Subset analysis revealed that the increased expression of CD21 by fetal/neonatal T cells occurred to a greater extent on the CD8$^+$ subset of T lymphocytes in comparison to CD4$^+$ subset (Fig. 4*b*).

Levels of sCD21. As there were more CD21$^+$ T cells in the fetal/neonatal circulation and T lymphocytes are considered the major source of plasma sCD21 (24), we measured the levels of sCD21 in fetal and neonatal plasma. Samples collected during this study as well as archived fetal plasma samples from very early in gestation (16–25 wk of gestation) were used. Plasma levels of the soluble form of CD21 showed a significant
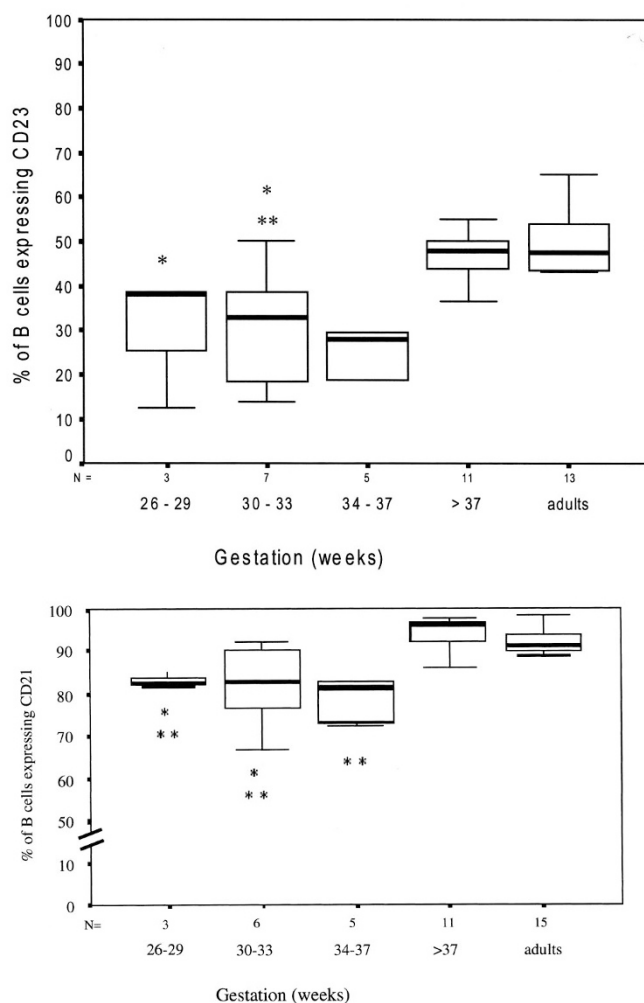
increase over gestation to be comparable to the adult by 34–37 wk of gestation (Fig. 5; $p = 0.007$, Kruskall-Wallis).

DISCUSSION

This is the first study to describe CD23 and CD21 expression by umbilical cord blood mononuclear cells at term (>37 wk of gestation) and preterm birth (26–37 wk of gestation). The percentages of CD23$^+$ or CD21$^+$ B cells were comparable between term samples and the adult, but there was clearly "maturation" of the percentage of B cells positive for CD23 and, to a lesser extent, CD21 over the third trimester of pregnancy. The most striking difference between the adult and fetal/neonatal samples was the increased percentage of CD3$^+$ T cells expressing CD21 and the reduced levels of sCD21 in the fetal circulation. Surface expression of CD21 by the CD3$^+$ population decreased in contrast to soluble levels that increased with increasing gestational age.

Membrane CD23 negatively regulates IgE production (21, 22, 25), whereas the soluble form (sCD23), derived by proteo-
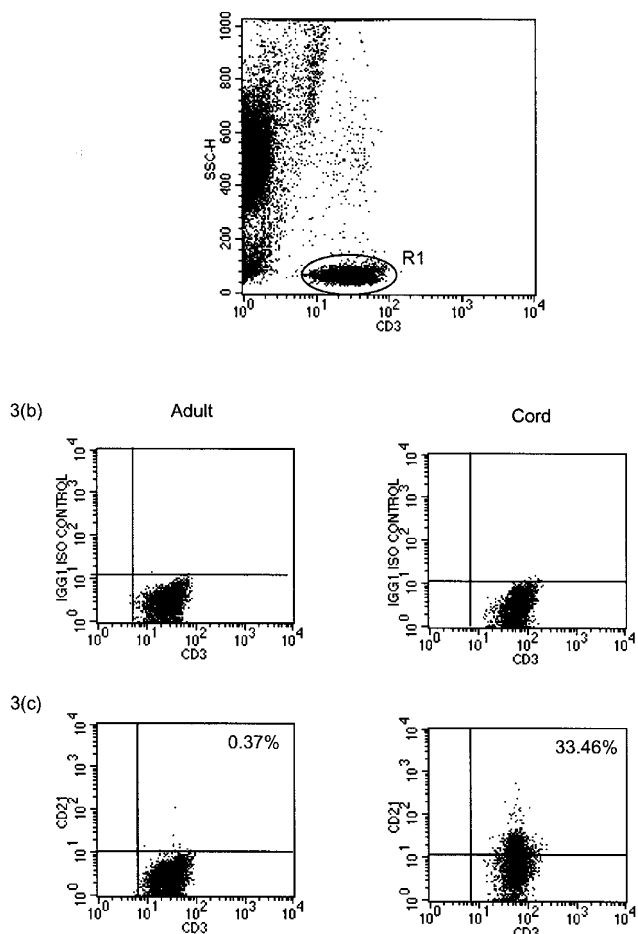
Figure 3. The identification of T cells expressing CD21. T cells were (*a*) identified by their characteristic side-scatter profile and CD3 positivity, and then 5000–10000 events (*R1*) were analyzed with phycoerythrin-conjugated (*b*) isotype control (mIgG1) or (*c*) anti-CD21. Examples of results obtained with cord and adult blood are shown.

Figure 4. The percentage of T cells expressing CD21 over gestation. Flow cytometry was used to determine the percentage of (*a*) CD3$^+$ T cells and (*b*) CD4$^+$ compared with CD8$^+$ T cells from fetuses/neonates of different gestation and adults expressing CD21. *Significant difference compared with adults ($p < 0.02$, see text for values); #significant difference between the percentage of CD4$^+$/CD21$^+$ compared with CD8$^+$/CD21$^+$ cells at the same gestation (*b*).

lytic cleavage (26), supports IgE production. This was best demonstrated in a recent study using human peripheral blood lymphocytes (25) in which inhibition of the release of CD23 from the cell surface inhibited IL-4-induced IgE production. Moreover, the release of sCD23 was found to precede IgE production. In the current study, the percentage of CD23$^+$ B cells as well as the density of expression, mean fluorescence intensity (data not shown), was similar in the adult and term neonate. Thus, it is unlikely that altered membrane CD23 expression is contributing to the very low levels of circulating IgE that occur in the neonate. In contrast to membrane CD23, sCD23 enhances IgE production (22, 25). Soluble CD23 levels were not examined in this study, but, in a previous study, cord sCD23 levels were reduced compared with the adult (27). As the processing of mCD23 to sCD23 may have an IgE-enhancing effect (25), restriction of this pathway on fetal/neonatal B cells could contribute to reduced IgE production.

The only other study to consider CD23 expression during gestation used RT-PCR to show that transcripts for both CD23a and b were present from as early as 8 wk of gestation in the liver, spleen, mesentery, and gut (9). Furthermore, approximately 70% of cord blood samples from the second
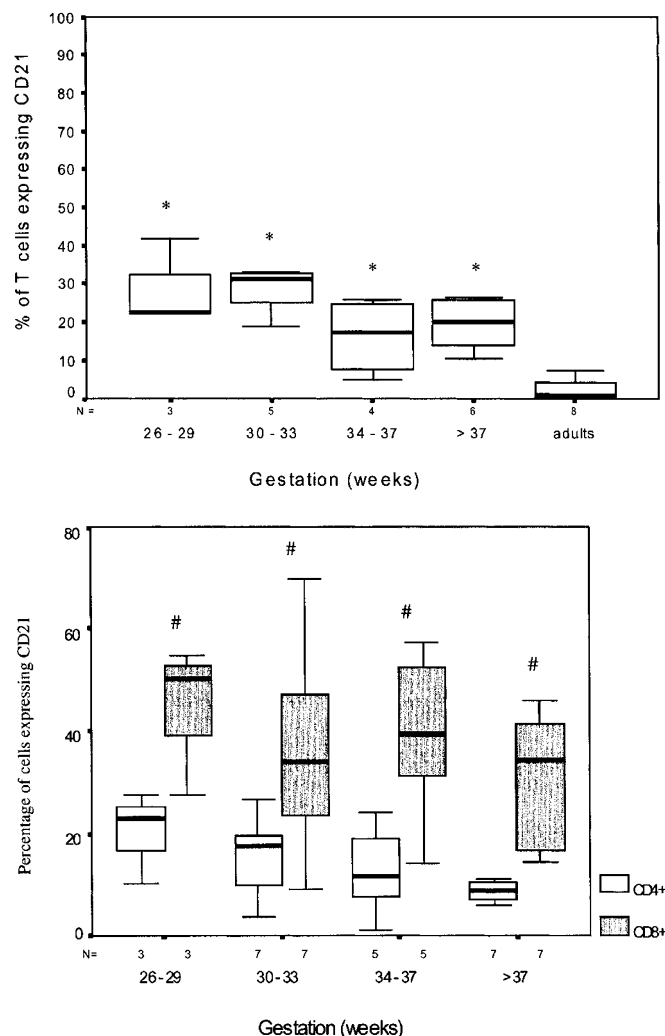
trimester (14–26 wk) contained transcripts for CD23a and CD23b. In the third trimester, nearly all samples expressed mRNA for CD23a and 60% expressed mRNA for CD23b. As we used flow cytometry to study CD23 expression, it is not possible to differentiate between the two isoforms of CD23, as they differ in the N-terminal cytoplasmic region, however, it is likely that the expression we were assessing on B cells is the constitutively expressed CD23a isoform.

The only CD23 ligand examined in this study was CD21. The number of B cells expressing CD21 clearly increased over gestation and, most strikingly, the percentage of T cells expressing CD21 was much higher than in adulthood. There are reports of the expression of CD21 by T cells from adult peripheral blood (28). However, other studies indicate that, although the levels of transcripts for CD21 are comparable between adult peripheral blood T and B cells (29), circulating adult T cells do not express detectable levels of membrane
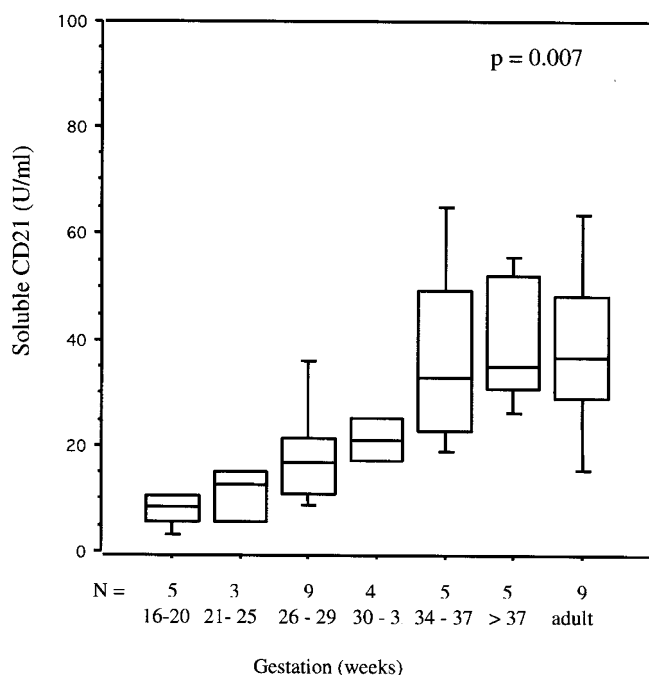
Figure 5. Plasma-soluble CD21. The level of soluble CD21 in plasma from fetuses and neonates of different gestational ages and adults was measured by specific ELISA. The trend to increased plasma sCD21 over gestation was significant ($p = 0.007$, Kruskall-Wallis).

CD21 (29, this study). Still, up to 70% of normal human thymocytes express CD21 (30, 31), and it has been suggested that CD21 could have a role in the proliferation and differentiation of T cells in the very early stages of maturation. Thus, the CD21 expression we observed on fetal/neonatal T cells could reflect the immaturity of the T-cell population, indicating recent emigration from the thymus. Other phenotypic markers, *e.g.* the greater percentage of CD38$^+$ T cells in the neonatal circulation (32), also indicate that cord blood T cells are immature.

To address this further, we considered the expression of CD21 by the CD4$^+$ and CD8$^+$ T-cell subsets in the fetal/neonatal blood as the expression of CD21 was more marked on CD8$^+$ compared with CD4$^+$ thymocytes (31). The percentage of CD8$^+$/CD21$^+$ cells was significantly greater than CD4$^+$/CD21$^+$, further supporting the postulate that the expression of CD21 by fetal/neonatal T cells is a marker of immaturity. The congruency of increased surface CD21 on the T cells and reduced circulating levels makes it tempting to speculate that the difference reflects changes in the pattern of cleavage of membrane CD21 in neonatal compared with adult T cells. Soluble CD21 is formed by protease-mediated cleavage of the extracellular portion of membrane CD21, and *in vitro* studies reveal a parallel decrease in surface expression with increasing levels in supernatants (24).

The comparable percentages of CD21$^+$ and CD23$^+$ B cells at term birth and adulthood make it unlikely (unless there are functional differences) that altered expression of these contribute to reduced IgE production by the full-term neonate. However, a common feature of the fetus/neonate may be reduced levels of proteolytic cleavage of both mCD21 and mCD23 that might limit IgE production. Although occupancy of CD21 on B cells (using MAb or sCD23) enhances IgE production (21), the effect of T-cell-associated CD21 on IgE production is unknown, so it is not possible to determine yet whether the CD21$^+$ T cells influence neonatal IgE production. Alternatively, CD21 expression by neonatal and fetal T cells might simply identify immature T cells, newly emerged from the thymus, that are poor producers of IL-4 and fail to up-regulate CD40L and thereby fail to support IgE switching. The production of other classes of Ig are also reduced in the neonate, yet are not regulated by CD21 and CD23. Thus, expression of CD21 by neonatal T cells as a marker of T-cell immaturity could be examined postnatally to monitor natural T-cell maturation and to learn whether this is concomitant with maturation of the ability of B cells to produce all classes of immunoglobulin.

CD23 and CD21 have biologic effects additional to those described for IgE production, including B-cell proliferation, antigen presentation, and the response to soluble antigen, T-B cell adhesion, and apoptosis (33–37). Further functional studies are necessary to elaborate whether CD21 and/or CD23 expression contribute to any of these functions in the neonate. This will be particularly important as CD23 and CD21 have other ligands. CD11b/CD18 is another ligand for CD23 (38) and additional ligands for CD21 include complement components C3d,g and iC3b, Epstein Barr virus, and interferon-α (39–41).

The low levels of circulating IgE at term and preterm birth and the diminished ability of neonatal B cells to produce IgE *in vitro* prompted our study. Interestingly, this may not be a universal property of B cells, as cord blood mononuclear cells from some neonates born in Kenya, where maternal parasitosis still occurs, produced relatively high levels of total and specific IgE (both *in vivo* and *in vitro*) (10). Thus, the low level of IgE production by the majority of neonates may ultimately reflect the absence of environmental/maternally derived factors that provide the trigger for IgE production that could manifest at the level of impaired IL-4 production and poor up-regulation of CD40L. A comparison of the regulatory factors involved in IgE production of infants born to mothers with and without parasitosis—especially T-cell maturity and, therefore, how T cell help might influence IgE production by B cells—during pregnancy would potentially reveal why IgE production by Western neonates is so low.

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