Co-stimulation of human decidual natural killer cells by interleukin-2 and stromal cells

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At the late secretory phase of the menstrual cycle and in early pregnancy, the uterine mucosa is infiltrated by large numbers of natural killer (NK) cells with a distinctive phenotype (CD56bright CD16– CD3–) and large granular lymphocyte (LGL) morphology. Circulating CD56bright NK cells generally proliferate in the presence of interleukin-2 (IL-2), but it is clear that cofactors besides IL-2 are required for optimal response. In the bone marrow, this co-stimulating signal is provided by stromal cells. In the present study we observe that uterine CD56+ cells from early pregnancy decidua similarly proliferate vigorously when cultured with decidual stromal cells and a sub-optimal dose of IL-2. This response is dependent on cell–cell contact, as no proliferation of decidual NK cells was observed when they were separated from stromal cells by a permeable cyclopore membrane. In addition, we have studied the expression of Bel-2 by decidual CD56+ cells. Our results show that the microenvironment of the uterus is likely to have a significant influence on the proliferation and survival of uterine CD56+ cells.

Key words: cytokine/microenvironment/uterine lymphocytes

Introduction

The establishment of the placenta in humans involves the migration of trophoblast cells into the mucosal lining of the uterus, the decidua. Associated with this trophoblast invasion is the presence of large numbers of bone marrow-derived leukocytes in the decidua (King and Loke, 1991; Loke and King, 1995). Leukocytes account for 30–40% of decidual cells (Bulmer et al., 1991), and are particularly prominent at the implantation site where they come into close contact with trophoblast cells (King et al., 1993). The composition of leukocytes in decidua is unusual. About 10–20% are CD3+ T cells (mainly TCR-α/β) (Mori et al., 1993), and there are approximately the same number of HLA-DR+ macrophages, whereas very few B cells are present. The most prominent population (70–80%) are natural killer (NK) cells with a distinctive phenotype (CD56bright CD16– CD3–) and large granular lymphocyte (LGL) morphology (Starkey et al., 1988; Nishikawa et al., 1990; King et al., 1991; Maruyama et al., 1992). Cells with a similar phenotype account for <1% of peripheral blood lymphocytes, implying that there is selective recruitment and/or inductive proliferation locally in the uterus in vivo. Proliferation of decidual leukocytes does occur in vivo (Pace et al., 1989; Tabibzadeh, 1990). By using double immunohistology for CD56 and a nuclear proliferation marker, Ki-67, we have established that this is mainly due to proliferation of the CD56+ NK cells (King et al., 1991). Interestingly, this NK cell proliferation is seen not only in decidua basalis where trophoblast is present but also in decidua parietalis, away from the implantation site. Furthermore, proliferation also occurs in non-pregnant luteal phase endometrium when other cellular elements in the uterine mucosa such as glandular epithelial and stromal cells have switched from a proliferative to a non-mitotic differentiated phenotype. The vigorous proliferation of CD56+ cells in the non-pregnant luteal phase indicates that this can occur in the absence of trophoblast and that the local uterine microenvironment could have an important influence.

In blood, the circulating CD56bright subset of NK cells proliferates in response to interleukin-2 (IL-2) alone without antigenic stimulation (Caligiuri et al., 1990; Nagler et al., 1990; Baume et al., 1992). Decidual CD56 NK cells behave in a similar manner (King et al., 1992). However, it is clear that, like T and B cells, NK cells require other cofactors besides IL-2 for optimal proliferation (Robertson et al., 1993). For example, NK cell proliferation is enhanced when B lymphoblastoid cells are present (Perussia et al., 1987) and NK cell maturation in the bone marrow is dependent on bone marrow stromal cells (Mrozek et al., 1996). We have therefore investigated whether decidual stromal cells could act as a cofactor for uterine NK cell proliferation. As a corollary to proliferation we have also studied the expression of Bel-2, a protein which prevents apoptotic cell death (Vaux, 1993) in CD56+ cells throughout the non-pregnant endometrium and decidua. Our results show that decidual stromal cells do influence the proliferation and survival of uterine CD56+ cells.

Materials and methods

Isolation of decidual stromal cells

First-trimester decidual tissue was obtained from vaginal termination of pregnancy and processed immediately. Tissues from 48 patients were used in 10 experiments to examine the proliferative effects of direct cell–cell contact. Tissues from 32 patients were used in eight experiments to look at the proliferative effects of cells separated by a permeable cyclopore membrane. With the exception of studies using autologous tissues, each experiment was performed using cells from a pool of three to six samples. Pieces of decidua compacts were identified macroscopically and stromal cells obtained and cultured in...
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RPMI 1640 medium/10% fetal calf serum (FCS; Gibco BRL Life Technologies Ltd, Paisley, UK) as described previously (Burrows et al., 1995). Fragments of decidua basalis containing trophoblast were not used. After overnight incubation of primary cultures in 25 cm² flasks the non-adherent lymphocytes were removed by washing. Cytospin smears made of the adherent cells were fixed with acetone (4°C for 5 min) and immunostained with a panel of antibodies as described (Table I) (Jokhi et al., 1993). On day 1, approximately 90% of the cells were stromal cells with about 10% of CD14+ macrophages. Endothelial cells and cytokeratin-positive epithelial cells accounted for <2%.

Isolation and culture of decidual lymphocytes

Decidual leukocytes were isolated from pooled fragments of decidua parietalis from first-trimester normal pregnancies as previously described (King et al., 1991). A mechanical method was used as this yields decidual lymphocytes with little stromal cell contamination. The lymphocytes were routinely cultured in RPMI medium with 10% FCS supplemented with 2 mM glutamine and antibiotics. After overnight culture, non-adherent lymphocytes were harvested from the culture flask, leaving behind adherent stromal cells and macrophages. Flow cytometric analysis of decidual lymphocytes prepared in this way revealed that 95% were CD45+, of which approximately 80% were CD56+ and 10–20% were CD3+ (Figure 1A and B).

A dose–response curve for the effect of human recombinant IL-2 (Sigma Aldrich Co. Ltd, Poole, Dorset, UK) on the proliferation of decidual lymphocytes, measured by [3 H]thymidine incorporation was established as described previously (King et al., 1992). Cells were grown at 2×10⁵/200 µl in RPMI 1640 + 10% FCS with or without IL-2 over a period of 10 days. At 16 h before the end of each time point, cells in triplicate wells of a 96-well tissue culture plate (Nunc; Gibco BRL Life Technologies Ltd) were spiked with 1 µCi [3 H]thymidine (Amersham Pharmacia Biotech Ltd, Rainham, Essex, UK). Cells were harvested using the Autowash 2000 cell harvester (Dynatech Ltd, Billingshurst, Sussex, UK). The average cpm from triplicate wells at each time point was compared. Viability counts of cells by trypsin blue exclusion were also made.

T-cell depletion from lymphocyte preparations

CD3+ T cells were depleted from lymphocyte preparations using AIS MicroCELLeCtector T-25 cell culture flasks (Applied Immune Sciences Inc., Labtech International Ltd, Uckfield, Sussex, UK) according to the manufacturer’s instructions. Lymphocytes were introduced into the flask and incubated for 1 h at room temperature, after which time the non-adherent CD3+ cells were collected. CD3+ T cells remained bound to the antibody-coated surface of the flask. The purity of these CD56+ cells was confirmed by flow cytometry (see later).

Co-culture of decidual lymphocytes with decidual stromal cells separated by permeable Cyclo pore membrane

After isolation and culture for up to 7 days, decidual stromal cells were treated with trypsin and transferred into plastic 15 mm-diameter tissue culture wells at 3×10⁵ cells/well in RPMI/10% FCS with or without 15 U/ml IL-2. After incubation for 4 h at 37°C (the time

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Figure 1. Flow cytometric analysis of isolated decidual lymphocytes, cultured overnight and stained with (A) anti-CD45FITC and anti-CD14PE, and (B) anti-CD3FITC and anti-CD56PE.
taken for the stromal cells to adhere firmly), 9 mm-diameter Cyclopopore cell culture inserts incorporating a 0.45 μm pore size permeable membrane (Falcon, Oxford, UK) and containing 2×10^6 decidual lymphocytes were gently lowered into the wells above the adherent cells. Control wells were assembled in which decidual lymphocytes were co-cultured with themselves in both the well and insert. After 80 h of culture, 5 μCi [³H]thymidine was added to each well and decidual lymphocytes harvested from the inserts after a further 16 h. The lymphocytes were transferred to a 96-well plate to facilitate harvesting with the cell harvester, as described previously. The cpm of all filter discs relating to each Cyclopopore insert were summed and compared.

**Co-culture of decidual lymphocytes in direct contact with irradiated decidual stromal cells**

Decidual stromal cells were treated with trypsin and plated at 4×10⁴ cells/well in a flat-bottomed, 96-well plastic culture plate (Nunc) with or without 5 or 15 U/ml IL-2. The whole culture plate was irradiated with 700 rads X-irradiation. Triplicates of irradiated and non-irradiated cells were plated to check irradiation efficiency. Decidual lymphocytes were added to the irradiated decidual stromal cells at 2×10⁴, 4×10⁴, 8×10⁴ and 1.6×10⁵ cells/well in triplicate, with or without 5 or 15 U/ml IL-2. Decidual lymphocytes were also plated in the absence of stimulator cells to give an indication of basal responder cell proliferation. After 80 h of culture, each well was spiked with 1 μCi [³H]thymidine. The cells were harvested after a further 16 h and the amount of incorporated radioactivity determined as described. The average cpm between triplicates of responder cells cultured with stroma was compared with that of responder cells cultured alone for each ratio and each dose of exogenous IL-2. Satisfactory irradiation of stimulator cells was verified as giving <10% of the count of non-irradiated cells both in the absence and presence of IL-2. The potential of the decidual lymphocytes used in each experiment to proliferate was assessed by their response to 100 U/ml IL-2 alone. The response of CD3⁻-depleted decidual NK cells was assayed in a similar manner.

**Flow cytometric analysis of responding lymphocyte populations**

Depletion of T cells using anti-CD3 monoclonal antibodies results in internalization of CD3. Therefore, T cells were detected by CD4 and CD8 staining. Decidual lymphocytes were double-labelled with CD8FITC/CD56PE and CD4FITC/CD8PE conjugated antibodies (Becton Dickinson Ltd, Oxford, UK) immediately following T-cell depletion and then after co-culture for 4 days with decidual stroma + 15 U/ml IL-2. Cells were incubated with antibody at 1/10 dilution for 30 min at 4°C, washed to remove unbound antibody, and fixed with 1% paraformaldehyde. Fluorescence-activated cell sorting (FACS) analysis was performed immediately, or after overnight storage at 4°C. Simultest control (Becton Dickinson) was used as a negative.

**Immunohistology**

Frozen sections of non-pregnant endometrium, decidua basalis and decidua parietalis were obtained as described previously (King et al., 1989). Cytosin preparations of decidual lymphocytes were made with a Shandon cyt centrifuge.

Dual immunohistology was performed to localize Bcl-2 and CD56 reactivity as described previously (King et al., 1996). The mouse monoclonal antibody to Bcl-2, 124 (culture supernatant, 1:5 dilution) was kindly provided by Prof. D. Mason, Oxford (Pezzella et al., 1990).

**Results**

Since all the cells used are from primary cultures with a range of gestational ages (6–12 weeks), the basal levels of [³H]thymidine incorporation inevitably show some variation between experiments. However, the same trend was always seen in each set of experiments. For each set of conditions the number of experiments performed has been given, and one representative set of data is shown. A standard t-test was used to evaluate the significance of differences between sets of triplicate data within each experiment.

**IL-2 time course and dose**

The first significant proliferative effect of IL-2 on decidual lymphocytes was noted at 25 U/ml, reaching a maximum at 75–100 U/ml. One unit of IL-2 is defined as the amount of IL-2 that is required to support half-maximal [³H]thymidine incorporation into CTLL-6 cells. Doses of IL-2 from 5–15 U/ml maintained approximately 70% cell viability (as shown by trypan blue exclusion) for 96 h, without inducing obvious proliferative effects. At 100 U/ml IL-2, [³H]thymidine incorporation peaked at 96 h of culture. This was followed by a second, similar peak at 144 h after the medium and IL-2 were replenished. Co-culture experiments were therefore centred around an expected 96-h response.

**Depletion of T cells from lymphocytes**

FACS analysis of CD3⁻-depleted lymphocytes revealed that NK cells comprised two distinct populations with respect to CD56 expression. Most were CD56bright and the remainder CD56dim (Figure 2A). CD56FITC/CD8PE double-labelling revealed that although 11.6% of the total cell population was CD8⁺, the vast majority of these cells were also CD56⁺ and therefore of NK cell phenotype. Only 0.4% of the total population were CD56⁻/CD8⁺ T cells (Figure 2A). CD8FITC/CD4PE double-labelling to separate T-cell subsets revealed that CD4⁺ T cells constituted only 0.5% of the total population (Figure 2B). It can also be seen that the CD56bright cells are CD8dim, whereas the CD56dim and CD56⁺ cells contain both CD8bright and CD8dim cells (Figure 2A).

**Decidual lymphocyte response to decidual stromal cells**

Contact with a monolayer of irradiated decidual stromal stimulator cells did not increase the incorporation of radioactive label by decidual lymphocytes in the absence of IL-2 (five out of five experiments) (Figure 3A). However, in the presence of only a low dose of exogenous IL-2 (5 or 15 U/ml) which alone induced virtually no proliferative effect, [³H]thymidine incorporation by pooled decidual lymphocytes cultured on decidual stroma was significantly higher than in the absence of stimulator cells (P < 0.001 in six of eight experiments) (Figure 3A and B). Importantly, this effect was still observed when decidual lymphocytes were depleted of CD3⁺ T cells (P < 0.001 in three of three experiments) (Figure 3C). To control for any possible effect of using allogeneic cells, autologous stromal cells were also isolated as stimulator cells. When these decidual lymphocyte responders from individual donor tissues were used, autologous as well as homologous decidual stromal cells were able to induce similar significant proliferative responses in the presence of low-dose IL-2 (15 U/ml) (P < 0.001 in five of five experiments) (Figure 3D). To determine if cell contact is required for proliferation, pooled
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Figure 2. Flow cytometric analysis of decidual lymphocytes depleted of CD3\(^+\) cells and stained with (A) anti-CD8\(^{FITC}\) (FL-1) and anti-CD56\(^{PE}\) (FL-2), and (B) anti-CD4\(^{FITC}\) (FL-1) and anti-CD8\(^{PE}\) (FL-2). The results are shown in lymphocytes before (A, B) and after (C, D) culture in contact with decidual stromal cells.

decidual lymphocytes co-cultured with decidual stromal cells, but separated from them by a permeable Cyclopore membrane, were analysed. There was no increased radioactive labelling compared with cells co-cultured without decidual stromal stimulator cells, even in the presence of low-dose IL-2 (15 U/ml) (no significant difference in eight of eight experiments; data not shown).

FACS analysis of responding lymphocytes
FACS analysis of CD3\(^+\)-depleted lymphocyte responders indicated that, after culture for four days in contact with decidual stroma + 15 U/ml IL-2, CD56\(^+\) NK cells were still predominant but the expression of CD56 was much less (compare Figure 2C with Figure 2A). The proportion of CD4\(^+\) T cells (0.5%) remained static (compare Figure 2D with Figure 2B), while the CD8\(^+\) subset increased slightly from 0.4% to 1.7% (compare Figure 2C with Figure 2A). This, and the inevitable small degree of contamination from detached stromal stimulator cells, accounted for the slight decrease in the overall percentage of NK cells (96% before co-culture, 89% after co-culture).

Immunohistology for Bcl-2
We have previously investigated the proliferation of uterine CD56\(^+\) cells in vivo by performing double immunohistology for CD56 and the proliferation marker Ki-67 (King et al., 1991). To investigate the presence of Bcl-2 in these cells, similar sections and cytopsin smears were double-stained with monoclonal antibodies to Bcl-2, (124), and to CD56, (Leu-19), which identifies uterine NK cells. Sections of decidua stained for Bcl-2 alone showed positive staining of nuclei in cells with the morphology and distribution typical of uterine NK cells (Figure 4A). Dual immunohistology showed that there were numerous strongly staining CD56\(^+\) Bcl-2\(^+\) cells (Figure 4B). Cytospin smears of decidual lymphocytes were also stained for Bcl-2, and cells with the characteristic reniform nuclear morphology of LGL were clearly positive. Most strongly stained were decidual NK cells which had been in culture for four days with 100 U/ml IL-2. Similar cells cultured in the absence of IL-2 were negative for Bcl-2 and showed features of apoptosis with nuclear disintegration and vacuolation (not shown).

Discussion
We have reported previously that decidual CD56\(^+\) lymphocytes proliferated in response to IL-2 in vitro in a dose-dependent manner, and that this activation occurred through the intermediate affinity receptor, IL-2R\(\beta\) (King et al., 1992). Similar
findings have been reported by others (Starkey, 1991; Saito et al., 1993). Thus, IL-2 appears to be as potent a mitogen for decidual NK cells as for circulating NK cells (Robertson et al., 1993; Carson et al., 1994; Warren et al., 1996). However, NK cells require contact with other stimulator cells together with IL-2 to achieve an optimal proliferative response (Warren et al., 1996; Robertson et al., 1996–7). The K562 cell line, B-lymphoblastoid cell lines and melanoma cell lines have all been shown to act as co-stimulators for NK cell proliferation. Cell–cell contact and metabolically active stimulator cells are...
necessary for proliferation, suggesting that receptiveness to IL-2 is induced actively by the stimulator cells (Warren, 1996). In the present study, we have made similar observations with decidual NK cells. We find that cell–cell contact is necessary, as no proliferation of NK cells with low-dose IL-2 was observed with decidual stromal cells separated by a semi-permeable membrane. As in other systems the decidual stromal cells do not initiate proliferation in the absence of IL-2. In addition, both autologous and homologous stromal cells are effective, so that the co-stimulatory signal is unlikely to be triggered by allogeneic recognition.

The molecular nature of the human NK cell stimulatory response is not yet clear, but does not appear to involve receptors which can co-stimulate T-cell proliferation such as CD2, CD28 and CD11a (Robertson et al., 1996–7). Recently, it has been shown that ligation of the NK lectin receptor, CD94, on blood CD56 bright cells and co-culture with IL-2 has been shown to augment the proliferative response (Voss et al., 1998). Interestingly, this effect was not seen with the major CD56 bright population; indeed, ligation of CD94 could even result in an inhibitory response which was variable among donors. Both blood and decidual CD56 bright cells are all CD94 bright Z199+, which correlates with the CD94/NKG2A phenotype (Verma et al., 1997), whereas CD56 dim cells have a much more heterogeneous expression of CD94/NKG2A which varies between donors (Perez-Villar et al., 1995, 1996). CD94 binds to HLA-E which is expressed on the cell surface if peptides derived from the signal sequence of some other classical HLA class I molecules are also present (Braud et al., 1997, 1998; X. López-Botet, personal communication), as would be expected to occur with decidual stromal cells.

Another possibility is that the unusual extracellular matrix, which is secreted under hormonal regulation by decidual stromal cells (Aplin et al., 1988; Loke et al., 1989; Zhu et al., 1992), influences NK cell proliferation. Decidual NK cells express integrins which are involved in binding to fibronectin and collagen (Burrows et al., 1993, 1995). Fibronectin has been observed to augment T-cell proliferation via binding to α5β1 and α3β1 receptors (Shimizu et al., 1990; Klingemann and Kohn, 1991).

The present study has clearly shown that IL-2 is important in decidual NK cell proliferation. However, the role of IL-2 in vivo is less clear because this cytokine has not been demonstrated at the implantation site (Saito et al., 1993; Jokhi et al., 1994a; King et al., 1995), nor in the non-pregnant endometrium (Lim et al., 1998). Furthermore, NK cells can proliferate during an early stage of a viral infection in vivo before the IL-2-producing, antigen-specific T cells are activated, indicating that this cytokine is not the primary stimulus for NK cells. It is now thought that IL-15 may substitute for IL-2 in vivo (Carson et al., 1994, 1995). IL-15 is produced by a range of non-T cells and, like IL-2, is capable of inducing NK cell cytotoxicity, proliferation and cytokine production. In addition, the IL-15R is a heterotrimeric molecule of which only the α subunit is specific to IL-15, while the β and γ subunits are common to the IL-2 receptor (Giri et al., 1995; Kennedy and Park, 1996). We have shown recently that IL-15 is produced by cells of the decidua and will induce proliferation and augment cytotoxic activity in decidual NK cells in vitro (S. Verma, unpublished results). Investigations are in progress in our laboratory to assess whether similar co-stimulatory responses occur with IL-15 as are shown for IL-2 in the present study.

The regulation of cell numbers in a tissue is a balance between proliferation and cell death. Morphological features of apoptosis were observed in uterine NK cells at two to three days premenstrually, giving rise to the misnomer ‘endometrial granulocytes’ (Hamperl and Hellweg, 1958). In the late-secretory endometrium of a pregnant woman, the uterine NK cells do not undergo apoptosis. Similarly, apoptosis is only seen in decidua in a failed pregnancy. Thus, pregnancy is associated with survival of uterine NK cells. In this study we demonstrate that CD56 high cells co-express Bcl-2 in decidua and proliferative phase endometrium; this confirms previous reports (Koh et al., 1995). Positive Bcl-2 staining was also seen in the secretory phase, but this appeared to become weaker premenstrually, although quantification is difficult using immunohistology. There is thus a balance in the uterine mucosa between proliferation and apoptosis. The reason that apoptosis of NK cells is triggered premenstrually and with pregnancy failure is unknown, but there is obviously a correlation with falling progesterone concentrations. Uterine NK cells do not express the progesterone receptor, so the effect is likely to be indirect, acting via stromal cells (Inoue et al., 1996; King et al., 1996). We have shown that decidual NK cells undergo apoptosis rapidly when cultured in medium alone, but survive with IL-2, and these surviving cells stain strongly for Bcl-2. IL-15 can also sustain NK survival at low concentrations, and this is associated with Bcl-2 expression (Carson et al., 1997).

In conclusion, proliferation and survival of uterine NK cells are influenced by contact with the decidual stromal cells. Further experiments are required to determine which factors mediate this interaction. However, stromal cells may influence NK cell biology in other ways. We have observed that co-culture with stromal cells increased the secretion of cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF) and leukaemia inhibitory factor (LIF) by decidual NK cells (Jokhi et al., 1994b). Thus, stromal cells may not act merely as a stimulus for NK cell proliferation but could also affect their biological function. It is of interest that the uterine mucosa is the only tissue where NK cells proliferate and survive in such large numbers. There is evidence that bone marrow stromal cells play an important role in NK cell development (Sitnicka and Hansson, 1992). Stromal cells in the decidua could provide a similar microenvironment for NK cells in the uterus.

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