Symposium

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Current update of fetal tolerance in human pregnancy

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면역학적으로 semi-allogeneic graft 혹은 non-self인 태아가 모체 자궁내에서 거부반응없이 유지되려면 2가지 상반된 기전이 적절히 조절되야 한다. 즉, 영양 (nutrition)과 산소공급 (oxygenation)을 위해 태반이 탈락막내 안착되어야하며 동시에 과도한 자궁내 침투를 막아 모체조직을 보호해야 한다. 태아에 대한 면역학적 관용기전은 아직 명확히 규명되지 않았지만 크게 두 가지 핵심기전 (key mechanism)이 중요하다. 과거에 강조되었던 선천면역적 측면은, 독특한 항원발현을 하는 융모외 영양모세포에 대한 NK (자연살상)세포의 항원인식결과, 살상기능이 억제됨으로서 태아가 관용된다. 여기에 최근 T 조절세포의 등장으로 후천성 적응면역계 (adaptive immunity)의 세포성 면역 (cellular immunity)이 중요한 기전으로 알려져있다. 과도한 자궁내 침투를 막기 위해 NK와 T 세포에 의한 영양모세포의 세포고사 (apoptosis)가 일어난 후 항원전달세포 (Antigen Presenting Cell)에 의해 포식 (phagocytosis)되고 다시 전달 (cross presentation)된 부체항원 특이관용이 일어난다. 여기에 IDO, IFN-γ , CTLA-4들의 발현이 증가된 조절성 T 임파구 (Treg cell) 등의 역할이 중요하다. 그러나 이 두 가지 핵심 기전외에도 무한히 복잡한 기전들이 계속 규명되어야만 인간 임신의 초기유지 과정이 이해될 것이다.

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uNK cells in pregnancy

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Uterine natural killer (uNK) cells appear in implantation sites with decidualization. Initially, they are rare, highly proliferative cells that become abundant by mid-gestation then die abruptly. Steps regulating the cyclic appearance of uNK cells are incompletely defined. Although progesterone (P4) has an essential role, mature uNK cells of women and mice lack progesterone receptors (PR). Immunohistochemical studies suggest mouse PR- uNK cells may co-localize with PR+ stromal cells while human PR- uNK cells co-localize with immature, DC-SIGN+ dendritic cells (DCs). DCs have the potential to produce progesterone-regulated interleukin (IL)-15, a growth factor essential for uNK cells. Since the high affinity IL-15Rα is presented to differentiating NK cells in trans, requiring cell contact, histologically-detected interactions may be of central importance for uNK cell differentiation. Thus, a pregnancy time-course, histological study of uNK cell differentiation and localization was undertaken in PR-LacZ transgenic mice. PR+ cells and uNK cells were co-localized using LacZ histochemisty and Dolichos biflorus (DBA) lectin staining, respectively. UNK cells appeared mesometrially, where PR+ cells were rare, at gestation day 5.5. UNK cells had limited, apparently random contact with PR+ cells throughout pregnancy and never themselves expressed PR. Thus, uNK cell differentiation does not appear to require contact with PR+ cells. Potential functions of human uNK cells at the fetal maternal interface are not yet clearly established to date, but several hypotheses are being evaluated, including control of extravillous invasion and uterine vascular remodeling, both are pivotal events for the normal process of pregnancy. uNK cells were believed to play a major role in all stages of preeclampsia development through a well-balanced production of pro-inflammatory cytokines and angiogenic factors which could then trigger the maternal disease. However, in the future, further studies are needed to improve our poor understanding of the role of uNK cells in the pathophysiology of preeclampsia.

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Effect of hypoxia on endothelial nitric oxide synthase, NO production, intracellular survival signalling (p-ERK1/2 and p-AKT) and apoptosis in human term trophoblasts

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Objective: The objective of the study was to evaluate the effects of hypoxia on eNOS, activation of intracellular survival signalling (p-ERK and p-AKT) and apoptosis in human term trophoblast

Study Design: Human term trophoblasts were isolated from term placentas of uncomplicated human pregnancies. Cytokeratin staining comfirmed cytotrophoblast (CT) cell type. CT cells were cultured in either 21% oxygen (control condition) or 2% oxygen (Hypoxia condition) for 24, 48, and 72 hours. At each time point eNOS, p-NOS (Ser1177), p-ERK and p-AKT protein were assessed by Western blot and apoptosis by dUTP nick end-labelling (TUNEL) assay. Media was collected for NOx determination at each time point.

Results:

Compared with control condition, CT cells exposed to hypoxia showed :

(1) decreased eNOS expression at 48hours ($p<.002$) and 72hours ($p<.02$);

(2) increased p-eNOS (Ser1177) expression at at 48hours ($p<.003$) and 72hours ($p=0.074$)

(3) no difference in the total NOx production ;

(4) increased p-ERK expression at 24 hours 48hours and 72 hours ($p<0.02$. $p<0.04$ and $p<0.04$, respectively);

(5) increased p-AKT expression at 24hours ($p<0.05$) and

(6) increased apoptosis at 48hours ($p<0.02$) and 72hours ($p=0.079$) ;

Conclusion:

These results suggest that hypoxia decreases eNOS expression but increases phospho-eNOS (Ser1177) expression in cultured human trophoblast and hypoxia increases activation of intracellular survival signalling expression in cultured human CT and hypoxia induced apoptosis is associated with insufficient activation of AKT.