The Role of Placental Cytokines in Regulation of Placental Hormone Secretion and Potentiation of Fetoplacental Defense Mechanism in the Intrauterine Inflammatory Disease

Noboru Matsuzaki, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodacho, Izumi City, Osaka 590-02, Japan

There are an increasing number of reports which show the production of various kinds of cytokines by a human placenta. Such cytokines include interleukin-1α (IL-1α) (1), IL-1β (1), tumor necrosis factor-α (TNF-α) (3), transforming growth factor-β (TGF-β) (4), IL-6 (5), IL-8 (6) and monocyte chemotactic and activating factor (MCAF). Since these cytokines possess multiple biological functions, I focused in the present symposium on the placental cytokine functions for their regulatory endocrine activities (2, 3, 6, 7) and potentiation of host (feto-placental) defense mechanism (1, 4, 5, 8-11).

Human trophoblasts in the first trimester were prepared according to the method described previously (6, 7) and stimulated with various kinds of cytokines after 2 days culture. The trophoblasts released human chorionic gonadotropin (hCG) in response to recombinant (r-) IL-1α (7), rIL-1β (7), rTNF-α (2) and rIL-6 (6). rIL-1β and rTNF-α independently stimulated trophoblasts to release IL-6 and augmented its release synergistically when both cytokines were added simultaneously (2). The released IL-6 subsequently stimulated hCG release by the trophoblasts. Such cytokine-mediated hCG release was blocked by rTGF-β in a dose-dependent fashion (3). We thus demonstrated the presence of a cytokine network among IL-1, TNF-α, TGF-β and IL-6 for placental hormone release in the first trimester.
placenta (3).

To investigate the ability of 2nd and 3rd placentas to produce various kinds of cytokines, we cultured the placentas for 24 hr which were vaginally delivered (with labor) and obtained by elective Caesarean section (without labor). We also cultured the placentas complicated with chorioamnionitis. The placentas with labor actively produced a higher amount of IL-1α and IL-1β than those without labor (1), but not the other placental cytokines such as IL-6, IL-8 and monocyte chemotactic and activating factor (MCAF). The placentas with chorioamnionitis produced a significantly higher amount of IL-1α (1), IL-1β (1), IL-6 (3), IL-8 (5) and MCAF than those with or without labor. Histochemical analysis of the placenta using specific monoclonal antibodies for the cytokines revealed that these cytokines were produced by trophoblasts and Hofbauer cells in the placenta (1, 4, 5). Northern blot analysis of the placenta with specific probes revealed the constitutive expression of mRNA for theses cytokines during pregnancy (5). Since IL-1 stimulates the synthesis of prostaglandin in the amniotic membrane and decidua, placental IL-1 might trigger the uterine contraction and onset of labor (1). In contrast, the placental IL-6 acts to heal tissue injury and reduce the systemic effect of infection and tissue damage (8). Moreover, the IL-6 stimulates synthesis of acute phase protein such as C-reactive protein (CRP) and potentiates fetomaternal immune system against the infection (8). Placental IL-8 in conjunction with placental MCAF stimulates neutrophils and monocytes to accumulate and be activated at the fetomaternal interspace in inflammation (5). These activated cells eliminate the invading bacteria by induction of
lysozomal enzyme release from the neutrophils (5).

To examine the nature of the cytokine cascade in the placenta with chorioamnionitis, we prepared the placental cells by Ficoll-Hypaque gradient sedimentation which contain trophoblasts and Hofbauer cells. These placental cells vigorously produced the inflammation-associated cytokines (IL-1, TNF-α, IL-6, IL-8 and MCAF) in response to lipopolysaccharide (LPS) in a dose-dependent fashion. The placenta cells activated by LPS produced a larger amount of IL-6, IL-8 and MCAF than the normal trophoblasts by stimulation with either rIL-1α or rTNF-α. The simultaneous stimulation of the placental cells with rIL-1α and rTNF-α resulted in additive, but not synergistic effect on IL-6 and IL-8 release by the placental cells. Stimulation of the placental cells with either rIL-6 or rIL-8 failed to produce any detectable amount of IL-8 or IL-6 reciprocally. The results demonstrated the independent signal transduction pathway are active for IL-6 and IL-8 release induced by IL-1 and TNF-α in the placenta.

In addition to the immunological states of the placentas with chorioamnionitis, we also examined the immunobiological states of the fetuses in an intrauterine infection (9-11). The cord sera from the babies with chorioamnionitis contained a larger amount of IL-6 and IL-8 than those without chorioamnionitis (9). These cytokines were found to be mainly derived from the placenta and the fetal immunocompetent cells activated by infectious stimuli. The IL-6 in the fetal serum acts to potentiate the synthesis of mRNA and protein for pulmonary surfactant protein-A (SP-A) to reduce the incidence of respiratory distress syndrome (RDS). The fetal serum IL-8, in contrast, acts to accumulate and
activate neutrophils at the inflammatory sites for elimination of the bacteria invading into the fetus. Interestingly, serum IL-8 level showed good correlationship with the stage of histological chorioamnionitis, suggesting that the serum IL-8 level can be used as a good marker for prenatal detection of chorioamnionitis (9).

Collectively, placental cytokines support the two major placental functions such as placental endocrine activity and fetoplacental defense mechanism during pregnancy.

Acknowledgement

The present work has been supported by the following members; Drs. Kouichirou Shimoya, Reiko Neki, Takayoshi Okada, Kaoru Yamanaka, Fumitaka Saji and Osamu Tanizawa in Osaka University Medical School, Osaka, 553 and Drs. Takashi Kameda and Takeshi Taniguchi in Osaka Rosai Hospital, Sakai, Osaka.

References


3. Matsuzaki N, Li Y, et al. (1992) Trophoblast-


