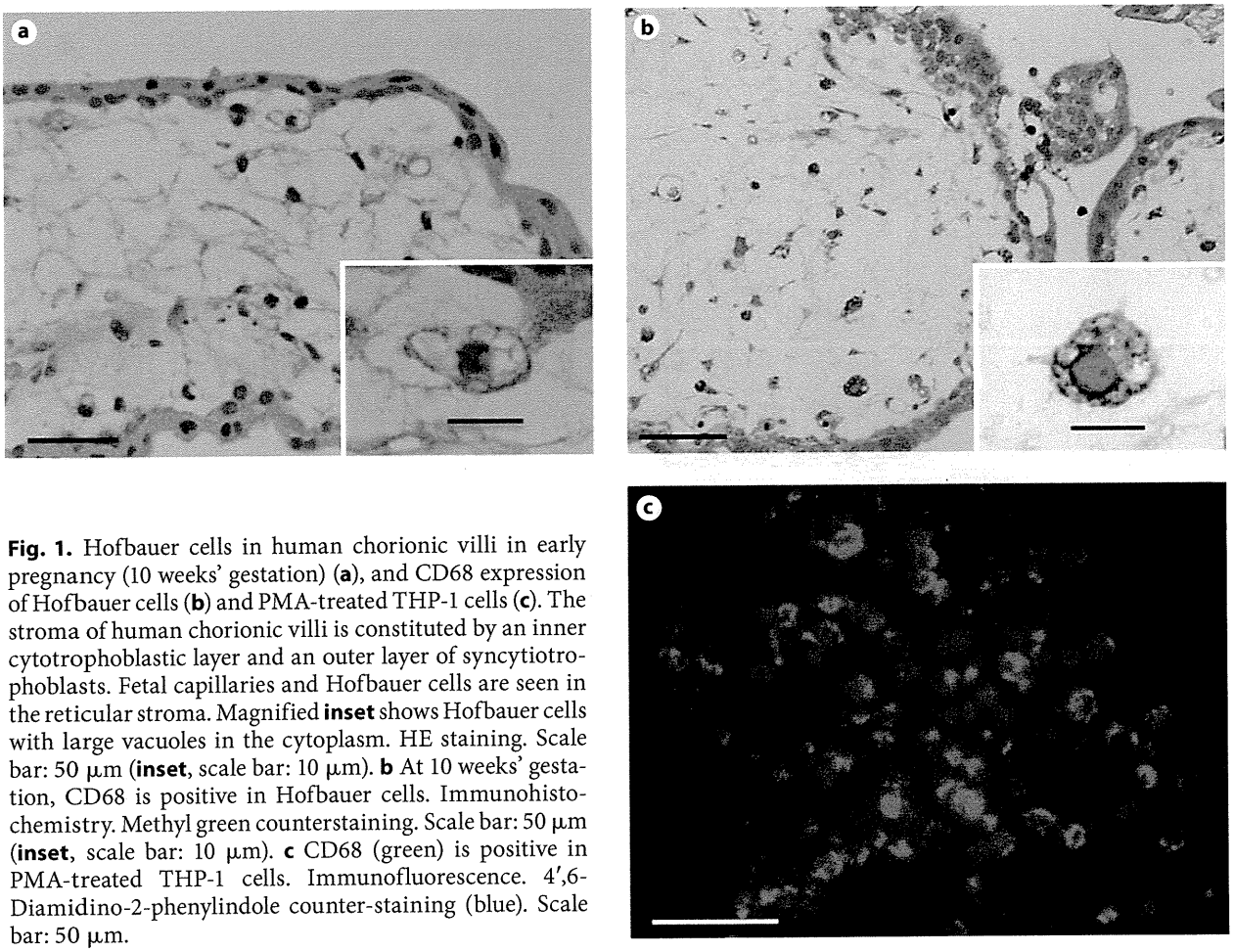

Fig. 1. Hofbauer cells in human chorionic villi in early pregnancy (10 weeks' gestation) (**a**), and CD68 expression of Hofbauer cells (**b**) and PMA-treated THP-1 cells (**c**). The stroma of human chorionic villi is constituted by an inner cytotrophoblastic layer and an outer layer of syncytiotrophoblasts. Fetal capillaries and Hofbauer cells are seen in the reticular stroma. Magnified **inset** shows Hofbauer cells with large vacuoles in the cytoplasm. HE staining. Scale bar: 50 μm (**inset**, scale bar: 10 μm). **b** At 10 weeks' gestation, CD68 is positive in Hofbauer cells. Immunohistochemistry. Methyl green counterstaining. Scale bar: 50 μm (**inset**, scale bar: 10 μm). **c** CD68 (green) is positive in PMA-treated THP-1 cells. Immunofluorescence. 4′,6-Diamidino-2-phenylindole counter-staining (blue). Scale bar: 50 μm.

1 and 2 h after hCG exposure (fig. 2d, e), and few vacuoles were observed at 3 h after hCG exposure (fig. 2f).

Selective Uptake of hCG by PMA-Treated THP-1 Cells

Immunocytochemistry showed that PMA-treated THP-1 cells before gonadotropin treatment were all negative against hCG, LH or FSH antibody (fig. 3a–c). On exposition to hCG for 1 min, hCG was positive in the cytoplasm of PMA-treated THP-1 cells (fig. 3d). In contrast to hCG, PMA-treated THP-1 cells showed negative staining with LH or FSH following exposure to LH or FSH in the same period (fig. 3e, f). Using specific oligonucleotide primer pairs in RT-PCR, we found that the expected hCG cDNA amplification products of 423 and 300 bp were not detected in both PMA-treated THP-1 cells without hCG and PMA-treated THP-1 cells 1 min after hCG exposure (fig. 3g). These results suggest that human macrophages are not involved in the production of hCG but in rapid and selective incorporation of hCG.

Endogenous LH/CG-R Δ9 Expression and Transient Reduced Expression by hCG in PMA-Treated THP-1 Cells

Immunocytochemistry demonstrated that LH/CG-R was strongly positive in the cytoplasm of PMA-treated THP-1 cells (fig. 4a). When the cells were exposed to hCG for 30 min, the cytoplasmic staining of LH/CG-R was weakened and cytoplasmic vacuoles appeared (fig. 4b).

A Western blotting analysis was conducted to determine the molecular size of the endogenous LH/CG-R. PMA-treated THP-1 cells expressed only a 60-kDa protein, designated as LH/CG-R Δ9 (fig. 5a). Next, the time course of LH/CG-R Δ9 expression was assessed after the administration of hCG. The expression of LH/CG-R Δ9 was transiently decreased from 30 min through 2 h after hCG exposure (fig. 5b). The reduction of LH/CG-R Δ9 was not induced by either LH or FSH exposure (fig. 6).

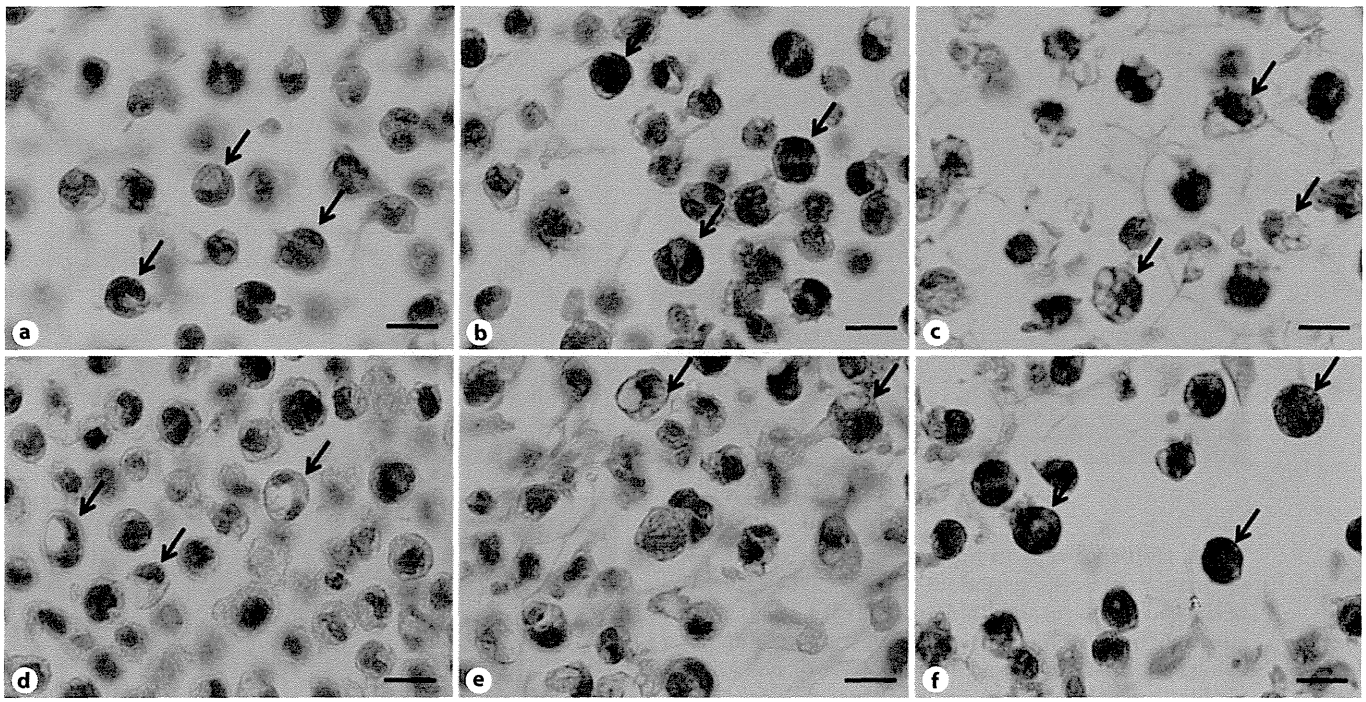

Fig. 2. Morphological changes in PMA-treated THP-1 cells after hCG exposure. PMA-treated THP-1 cells were exposed to 1,000 mIU/ml of hCG without hCG treatment (**a**), 15 min after hCG exposure (**b**), after 30 min (**c**), after 1 h (**d**), after 2 h (**e**), after 3 h (**f**). Few cytoplasmic vacuoles are seen in **a**, **b** and **f**. Multiple cytoplasmic vacuoles of various sizes are observed in **c**, and large vacuoles are partly seen in **d** and **e**. HE staining. Arrows indicate characteristic morphological feature in each panel. **a–f** Scale bar: 10 μm.

Discussion

Hofbauer cells are capable of both nonimmune and immune phagocytosis [Fox and Sebire, 2007a]. The placenta lacks a lymphatic system to return proteins from the interstitial space to the blood vascular system; therefore, intracytoplasmic vacuoles in Hofbauer cells have been considered to be associated with phagocytic activity to reduce serum proteins contained in the villous stroma and regulate the water in early placenta [Castellucci and Kaufmann, 2006]. They can also trap maternal immunoglobulins crossing over into the placental tissues and suppress the immune response to fetal transplantation antigens [Frauli and Ludwig, 1987; Fox and Sebire, 2007a]. Hence, it has been postulated that Hofbauer cells act as a secondary line of defense to prevent pathogens and toxins from reaching the fetus [Ingman et al., 2010]. Since excess hCG also has an adverse effect on the fetus, we hypothesized that Hofbauer cells phagocytose and regulate hCG and also that their peculiar cytoplasmic vacuoles are related to their cell-specific function. The present study first demonstrated that hCG elicited transient morphological changes, mimicking Hofbauer cells in PMA-treated THP-1 cells, suggesting that characteristic vacuoles in Hofbauer cells are associated with hCG-phagocytic activity.

The major role of hCG in early pregnancy is to maintain the corpus luteum for persistent progesterone production [Shi et al., 1993; Cunningham et al., 2005]. hCG is produced and secreted from placental syncytiotrophoblasts into the maternal circulation and is detectable in maternal plasma 7–10 days after implantation of the fertilized ovum. The maternal serum hCG levels rise very rapidly, to reach a transient peak at about 8–10 weeks of gestation. The level in this period is 1,000 times greater than the level 6 weeks earlier [Fox and Sebire, 2007b]. The levels of hCG begin to decline, and a nadir is reached by about 20 weeks of gestation. The plasma levels are maintained at this lower level for the remainder of pregnancy [Cunningham et al., 2005]. Circulating maternal hCG at the peak level enters in the fetal plasma and stimulates fetal testicular testosterone production. hCG acts

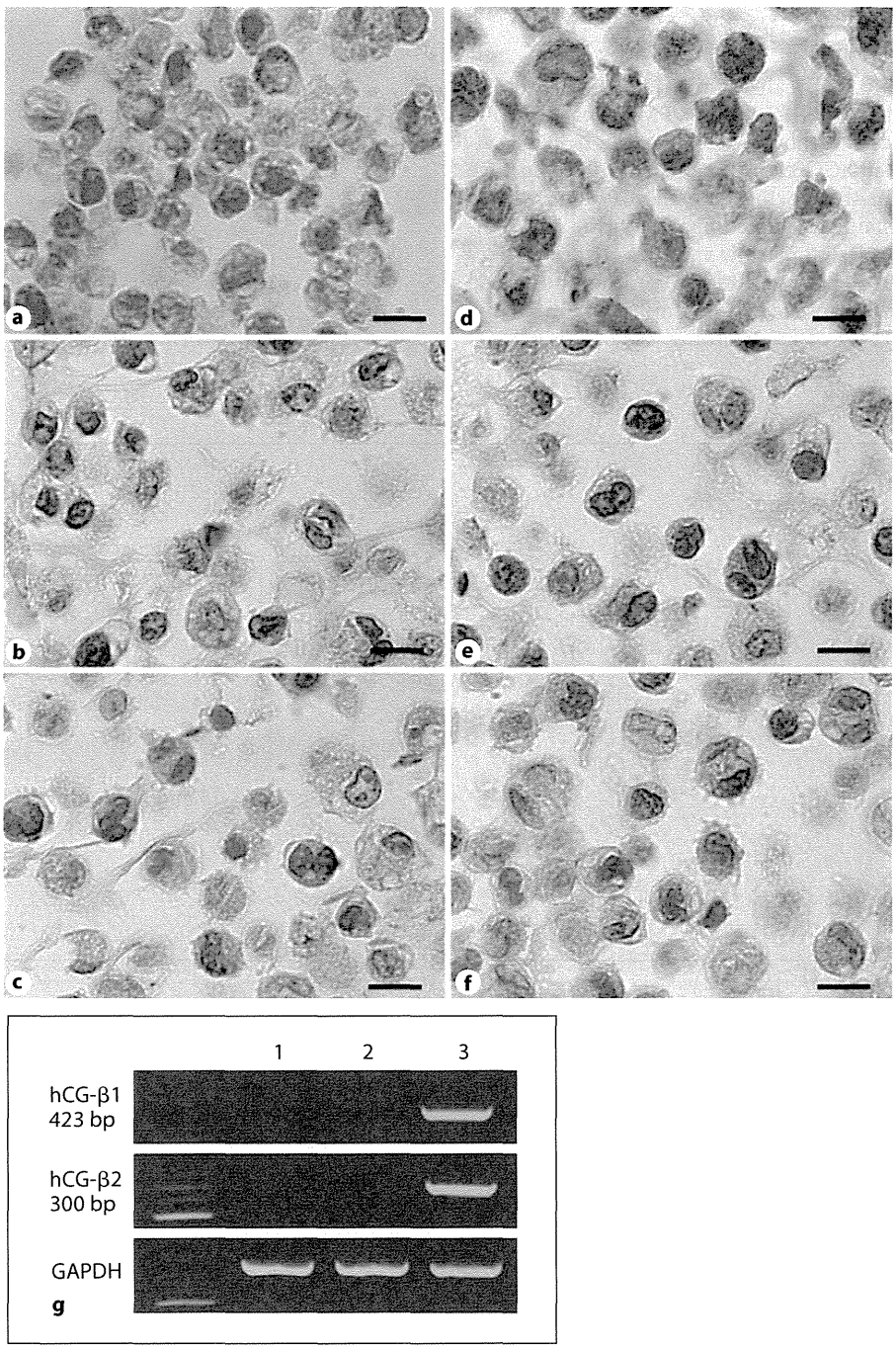

Fig. 3. Localization of gonadotropin and expression of hCG-β mRNA in PMA-treated THP-1 cells after gonadotropin exposure. **a–c** PMA-treated THP-1 cells without gonadotropin treatment. **d–f** PMA-treated THP-1 cells exposed to hCG (**d**), LH (**e**) or FSH (**f**) for 1 min. **g** Expression of hCG-β mRNA in PMA-treated THP-1 cells without hCG treatment (lane 1), PMA-treated THP-1 cells exposed to hCG for 1 min (lane 2) and the chorionic villi (lane 3) analyzed by RT-PCR. The cells were immunostained with anti-hCG-β antibody (**a**, **d**), anti-LH-β antibody (**b**, **e**) or anti-FSH-β antibody (**c**, **f**). **d** shows positive staining in the cytoplasm and the other panels all show negative staining. Neither hCG-β1 nor hCG-β2 mRNA is expressed in lanes 1 and 2. cDNA of the chorionic villi was amplified with primer for 423 and 300 bp showing the predicted hCG-β DNA products as positive control (lane 3). GAPDH was used as a control. Methyl green counterstaining. Scale bar: 10 μm.

as an LH surrogate and stimulates replication of testicular Leydig cells and testosterone synthesis to promote male sexual differentiation at a critical time in sexual differentiation of the male fetus [Huhtaniemi et al., 1977; Cunningham et al., 2005]. High-dose hCG exposure to mice offspring induce abnormal male and female gonadal development [Takasugi et al., 1985; Matzuk et al., 2003]; therefore, exposure to excess hCG has the possibility to cause ambiguous genital differentiations of human fetuses. In addition, the cytoplasm of Hofbauer cells is coarsely vacuolated during early pregnancy; however, as gestation progresses, the vacuoles decrease in number

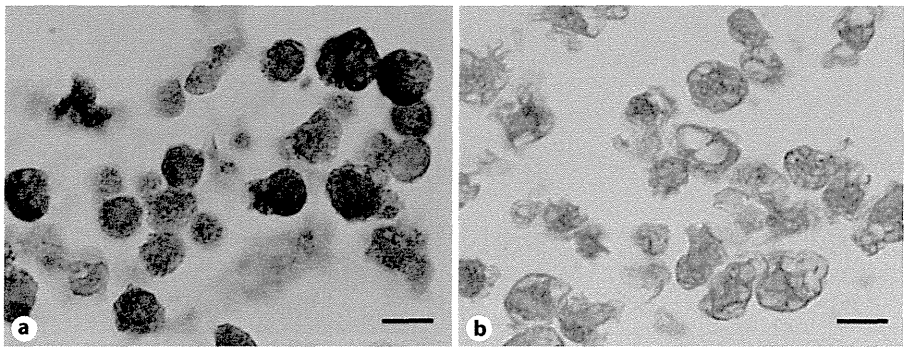

Fig. 4. Localization of LH/CG-R in PMA-treated THP-1 cells. **a** PMA-treated THP-1 cells without hCG treatment. **b** 30 min after hCG exposure, LH/CG-R is positive in their cytoplasm. LH/CG-R is weakly stained when compared with **a** and multiple cytoplasmic vacuoles of various sizes are observed. Both were immunostained with anti-LH/CG-R antibody. **a**, **b** Methyl green counterstaining. Scale bar: 10 μm.

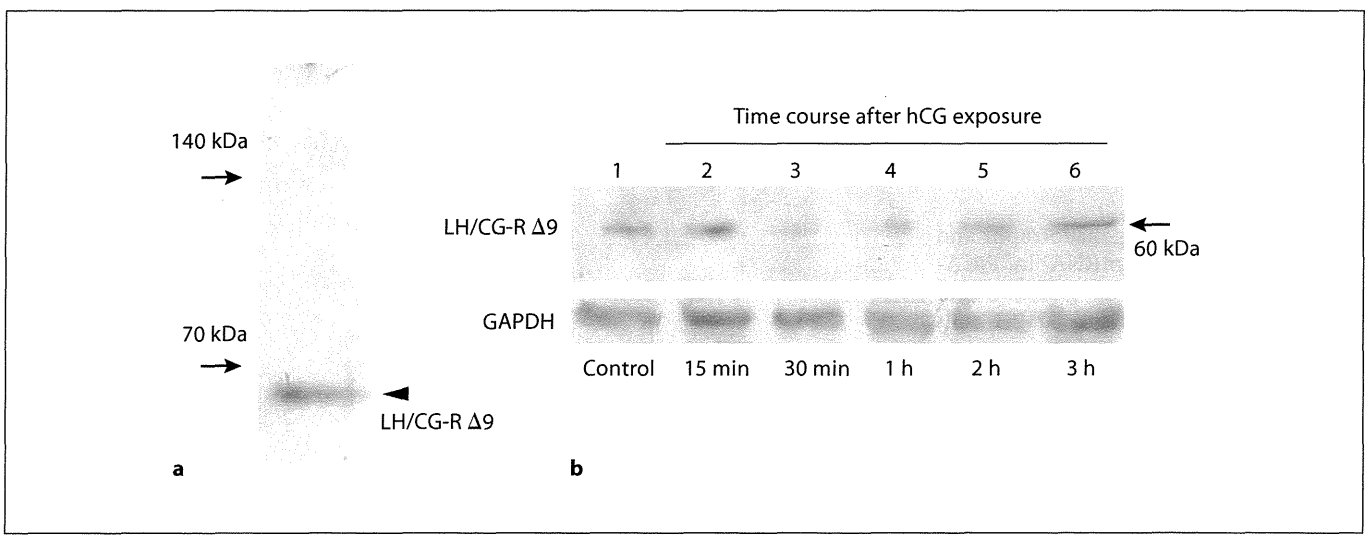

Fig. 5. Molecular weight and quantitative variation in LH/CG-R expression in PMA-treated THP-1 cells after hCG exposure. **a** LH/CG-R expression in PMA-treated THP-1 cells without hCG treatment. The arrowhead shows a protein band of 60 kDa. **b** Time course analysis of LH/CG-R expression in PMA-treated THP-1 cells after hCG exposure. Lane 1: control, lane 2: 15 min, lane 3: 30 min, lane 4: 1 h, lane 5: 2 h and lane 6: 3 h. The immunoreactive protein bands of lanes 1, 2, and 6 are visible; in contrast, those of lane 3, 4, and 5 are practically invisible. GAPDH was used as a control for protein loading.

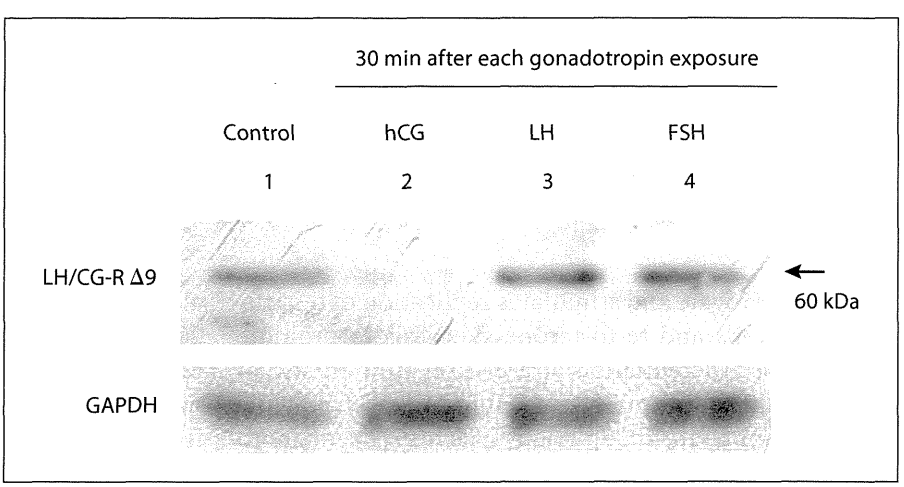

Fig. 6. Expression of LH/CG-R in PMA-treated THP-1 cells after exposure to gonadotropin. LH/CG-R expression in control (lane 1) and PMA-treated THP-1 cells 30 min after exposure to hCG (lane 2), LH (lane 3), or FSH (lane 4). The expression of LH/CG-R is decreased in only lane 2 compared with the control band. GAPDH was used as a control for protein loading.

and size [Castellucci and Kaufmann, 2006]. These findings indicate that the increased maternal hCG level is correlated with the increased number and size of vacuoles in Hofbauer cells. The correlation suggests that macrophages regulate peak levels of hCG during the first trimester and subsequently form characteristic cytoplasmic vacuoles.

In the present study, PMA-treated THP-1 cells quickly incorporated hCG, but not LH or FSH. This result suggests that human macrophages can distinguish hCG from LH or FSH on the cell surface. hCG, LH and FSH are dimers composed of two glycosylated polypeptide subunits, α and β. All of these human gonadotropic hormones share a common α-chain; therefore, the β-subunit determines the specific biologic activity of a glycopeptide hormone. hCG has the largest β-subunit, containing a larger carbohydrate moiety and 145 amino acid residues, including a unique carboxyl-terminal tail piece of 29 amino acid. Besides, hCG-β contains four additional sites for glycosylation in comparison with LH and FSH. This glycosylation makes hCG-β more negatively charged [Marc and Leon, 2011]. In early atherosclerotic lesions, macrophages do not take up native low-density lipoprotein but negatively charged oxidized low-density lipoprotein recognized by their scavenger receptors, subsequently forming foam cells [Steinberg and Witztum, 2010]. Intact hCG is more negatively charged in the early stage than in the late stage of gestation [Medeiros and Norman, 2009]. Human macrophages may recognize and incorporate more negatively charged hCG via transmembrane receptors, e.g. scavenger receptors.

The β-subunits of both hCG and LH have a high affinity for LH/CG-R, which plays a pivotal role in reproductive physiology [McFarland et al., 1989]. LH/CG-R is a 7-transmembrane receptor found on testicular Leydig cells, and on ovarian theca, granulosa, luteal, and interstitial cells. The receptor is also found in the human uterus, placenta, umbilical cord, sperm and ovarian neoplasm. This receptor is also expressed in the lymphocytes from pregnant women and macrophages derived from term decidua [Katabuchi and Ohba, 2008]. In the chorionic villi of the human placenta, syncytiotrophoblasts and Hofbauer cells are positively immunostained with anti-human LH/CG-R antibody, which was raised against the exon 1-mapping extracellular domain of LH/CG-R of humans [Sonoda et al., 2005]. The present study showed that the cytoplasm of PMA-treated THP-1 cells was positively stained with this antibody.

In addition to the full-length LH/CG-R mRNA, multiple splicing variants of LH/CG-R mRNA are expressed that originate from a single gene encoding LH/CG-R in gonadal porcine, rat and human tissues [Loosfelt et al., 1989; Koo et al., 1994; Themmen and Huhtaniemi, 2000]. The human ovary and placenta express two forms of LH/CG-R mRNA, full-length LH/CG-R and LH/CG-R Δ9 [Minegishi et al., 1997]. Although these splicing variants of LH/CG-R seem to be conserved among mammalians, the physiological role of the gene products remains unknown. PMA-treated THP-1 cells express only an mRNA encoding LH/CG-R Δ9; however, it is unclear whether endogenous protein is synthesized from this mRNA. The present study revealed that PMA-treated THP-1 cells expressed only a 60-kDa protein designated as LH/CG-R Δ9. This molecular size was consistent with that of translated product expressed in mammalian 293 cells transfected with cDNA encoding human LH/CG-R Δ9; on the other hand, those transfected with cDNA of full-length LH/CG-R express two molecular bands of 85 kDa (mature band) and 68 kDa (immature band) [Nakamura et al., 2004]. This is the first report to demonstrate the endogenous production of the splicing variant of LH/CG-R protein.

Few reports have speculated on the function of human LH/CG-R Δ9. Rat LH/CG-R Δ9 is capable of binding hCG but is trapped in an intracellular compartment [Segaloff and Ascoli, 1993]. The extracellular domain of rat or human LH/CG-R without exon 9–11 has a high affinity for hCG because this domain shows a remarkable correspondence to leucine-rich repeats; therefore, human LH/CG-R Δ9 is thought to have high affinity for hCG [Ascoli et al., 2002]. The labeled human LH/CG-R Δ9 protein is not expressed on the cell surface in mammalian 293 cells [Nakamura et al., 2004]. The role of LH/CG-R Δ9 in human ovarian steroidogenic cells may be to control the function of full-length LH/CG-R in a dominant negative manner by forming heteromeric complexes with full-length LH/CG-R which acts as a signal transducer [Nakamura et al., 2004]; in contrast, the roles of LH/CG-R Δ9 in PMA-treated THP-1 cells must be different from those of LH/CG-R Δ9 coexpressed in human ovarian steroidogenic cells because PMA-treated THP-1 cells do not express the gene encoding the full-length LH/CG-R. We demonstrated that hCG induced a transient reduction in endogenous LH/CG-R Δ9 in PMA-treated THP-1 cells that was synchronous with the appearance of vacuoles. No such reduction in LH/CG-R Δ9 was induced by LH or FSH exposure, thus suggesting that LH and FSH cannot be incorporated into PMA-treated THP-1 cells and bound to cytoplasmic LH/CG-R Δ9. This hCG-induced transient reduction in LH/CG-R Δ9 led us to hypothesize that the intracellular

receptor with affinity for hCG recognizes hCG incorporated into the cytoplasm and transfers it to lysosomes for degradation, and LH/CG-R Δ9 may be subsequently replaced in the cytoplasm by protein synthesis. Moreover, human macrophages may represent cytoplasmic vacuoles mimicking the structure of Hofbauer cells while they are degrading hCG in lysosomes. In the present study, we did not investigate primary Hofbauer cells but PMA-treated THP-1 cells, a macrophage cell line. Hence, further studies on Hofbauer cells isolated from the chorionic villi are needed to elucidate the mechanism.

In conclusion, hCG temporarily induced both peculiar vacuole formation, morphologically mimicking Hofbauer cells and decreased expression of endogenous LH/CG-R Δ9 in human macrophages, which selectively incorporated hCG into the cytoplasm. Hofbauer cells may regulate hCG via cytoplasmic LH/CG-R Δ9 at the feto-maternal interface by the same mechanisms demonstrated in this study, and their characteristic vacuoles may be associated with the cell-specific function to protect the fetus from exposure to excess maternal hCG during pregnancy.

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VI 絨毛性疾患

胞状奇胎の画像診断

Ultrasonographic findings of early-stage hydatidiform mole

大場 隆[1] 三好潤也[2] 片渕秀隆[1]

Key words：胞状奇胎，超音波断層法，妊娠早期胞状奇胎，間葉性異形成胎盤

はじめに

現在，胞状奇胎を画像診断するうえでの問題点は2つある．一つは妊娠早期における胞状奇胎の診断，もう一つは妊娠中期以降も生存している胎児を伴った胞状奇胎の鑑別診断である．

1 妊娠早期胞状奇胎の画像診断

妊娠早期の胞状奇胎(妊娠早期胞状奇胎)は胞状化しておらず，multivesicular patternを呈さない．妊娠の経過とともに一部の絨毛が小さな嚢胞を形成するようになり，これが徐々に増大して胞状奇胎の典型的な像を呈すると考えられている．胞状化が起こる前に子宮内容除去術が行われた場合，その症例は胞状奇胎として扱われず，続発する絨毛がんが見逃される恐れがある．妊娠早期の胞状奇胎が看過されているという指摘は以前からあり[1,2]，著者らが行った検討でも，民間医療機関で経験された胞状奇胎の62％は自然流産として扱われていた[3]．

1) 全胞状奇胎

全胞状奇胎は胎嚢を欠くため，hCG定量法と組み合わせることにより正常妊娠でないことを診断するのは容易である．妊娠早期からmultivesicular patternを呈する症例もあるが，多くの症例では嚢胞は観察されず，子宮内のエコーフリースペースを伴って，肥厚した絨毛が子宮内腔方向へ不規則に膨隆している(**図1-a**)[4]．全胞状奇胎では卵黄嚢や羊膜，そしてdouble sac signと呼ばれる絨毛膜と脱落膜との境界を欠くことが鑑別の指標となるが，一見すると胎嚢様の構造を伴うこともある(**図1-b**)．絨毛と筋層との境界は比較的明瞭である．

2) 部分胞状奇胎

子宮内に胎嚢，卵黄嚢，ついで胎芽が観察されたのちに絨毛の嚢胞化が認められることが多い(**図2-a**)．一般に部分胞状奇胎の胎芽は三倍体であるため妊娠初期に子宮内胎児死亡に至るが，その時点で絨毛が典型的なmultivesicular patternを呈していない場合は，病理組織学的検討が行われないかぎり自然流産として扱われてしまう．

部分胞状奇胎の画像所見は全胞状奇胎より多彩である[5,6]．妊娠早期全胞状奇胎の正診率は近年になって9割近くに高まってきたが，依然として部分胞状奇胎の6-8割は枯死卵あるいは稽留流産と臨床診断されており[7]，逆に胎芽や胎児を伴わず，画像所見だけでは全胞状奇胎と鑑別できない場合もある．一方で正常妊娠が過剰診断される恐れもある(**図2-b**)．胎児が生存している場合には部分胞状奇胎を疑っても安易な説明は避け，超音波断層法とhCG定量による慎重な経過観察が望ましい．

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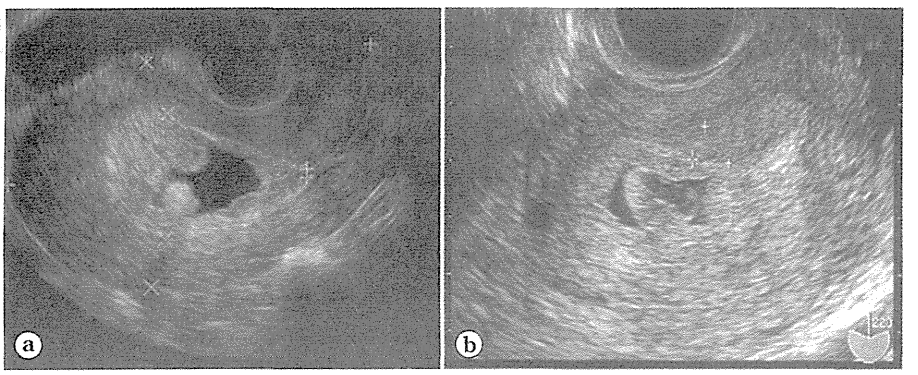

図1 妊娠早期胞状奇胎の経腟超音波断層法所見：全胞状奇胎

a. vesicleは観察されず，子宮内のエコーフリースペースを伴って，肥厚した絨毛が子宮内腔に向けて不規則に膨隆している．

b. 子宮内に胎嚢様の構造を認めるが，壁が厚く不整で，卵黄嚢や胎芽は観察されない．

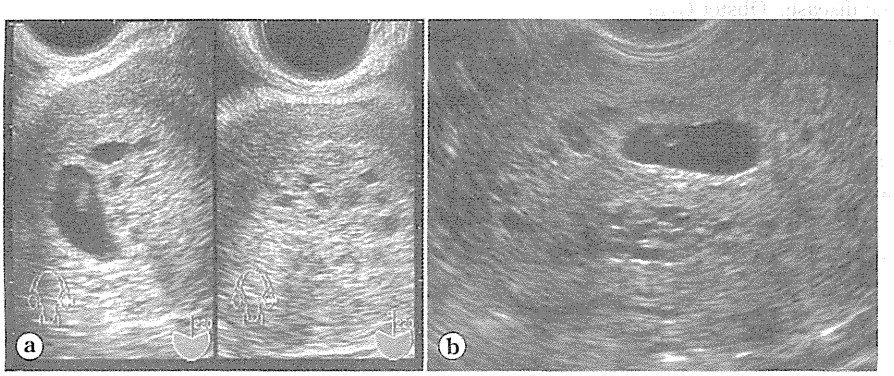

図2 妊娠早期胞状奇胎の経腟超音波断層法所見：部分胞状奇胎

a. 部分胞状奇胎(妊娠10週)：胎芽の心拍は認められない．

b. 正常妊娠(妊娠6週)：絨毛膜の外周に沿って胞状構造を認めたが，正常妊娠であり生児を得た．

2 妊娠中期以降の胎児を伴う胞状奇胎の鑑別診断

妊娠中期になっても胎児が生存し絨毛がmultivesicular patternを呈する場合には胎児共存奇胎や間葉性異形成胎盤(placental mesenchymal dysplasia: PMD)などとの鑑別を要する．

胎児共存奇胎は正常な胚と全胞状奇胎の二卵性双胎であり，胎児は正常に発育するが，妊娠を継続しても妊娠高血圧症候群を合併する危険が高く，早産に至ることが多い．更に約50％の症例は絨毛性疾患を続発する[8]ため慎重な対応が求められる．hCGが異常高値で，MRIによって正常絨毛領域とmultivesicleな絨毛の領域が明瞭に区別されることが診断の手がかりとなる．

PMDもまた胞状奇胎の診断を行ううえで留意を要する病態である．PMDは，超音波断層法にて胎盤の嚢胞状変化を呈し，組織学的に胞状奇胎とは異なる胎盤の形態異常として1990年代になって報告され始めた．2010年までの我が国における症例報告は30余例だが，実際の頻度は4,000–5,000妊娠に1例と推定される[9]．超音波断層法では妊娠中期以降に胎児とともに

肥厚した胎盤が認められ，その実質内に大小不整な嚢胞や管腔様構造を呈して胎児共存奇胎や部分胞状奇胎との鑑別を要する．PMDの自然史は今後明らかにされるべき課題である．

おわりに

近年の超音波断層法によって発見される妊娠早期の胞状奇胎は胞状化しておらず，超音波断層法所見も多彩である．最近改訂された絨毛性疾患取扱い規約[10]において，胞状奇胎の診断は組織学的所見に基づくことが明記された．すべての流産絨毛に対して，全胞状奇胎を鑑別診断するための組織学的診断あるいは遺伝学的解析が求められる．

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