IS-MW-1-4 Four pathological subtypes of high-grade serous adenocarcinoma of ovary, Fallopian tube and peritoneum indicate distinct clinical features and prognosis

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[Objective] High-grade serous adenocarcinoma (HGSAC) is classified to 4 subtypes based on gene expression profiles. We identified pathological classification according to these subtypes : Immuno-reactive (IR), Mesenchymal Transition (MT), Solid and Proliferative (SP) and Well Differentiated (WD). The aim of this study is to identify distinct clinical findings among 4 pathological subtypes of HGSAC. [Methods] The clinical factors of 69 HGSAC cases (IR : 18, MT : 27, SP : 17, WD : 7), which were treated at our institution were analyzed retrospectively.IC was obtained from all participants. [Results] The origin of all IR cases was ovary or Fallopian tube ($p=0.0279$). IR cases showed significantly earlier stages and possessed less peritoneal dissemination, omental cake and distant metastasis compared with the other subtypes ($p<0.01$ for all). MT included more cases of peritoneal origin, advanced stages, peritoneal dissemination and distant metastasis ($p<0.05$ for both). SP cases tended to include larger amount of ascites ($p=0.0592$) and magnetic resonance images demonstrated that a larger proportion of SP cases (11 out of 16) shows solid appearance compared with the other subtypes (29 out of 52, $p=0.3562$). [Conclusion] The pathological subtypes of HGSAC show distinct clinical behaviors. These findings lead to development of novel diagnostic tools and therapeutic strategies based on precision medicine.

IS-MW-2-1 Branched-chain amino acids regulate insulin-like growth factor binding protein-1 production by decidua and influence trophoblast migration

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[Objective] Insulin-like growth factor binding protein-1 (BP-1) is a major product of decidua and regulates extravillous trophoblast (EVT) migration. Branched-chain amino acids (BCAA) are known to regulate production of BP-1 in hepatic cells, however it is unknown whether BCAA also regulate BP-1 secretion in decidua. We examined possible changes in BP-1 production in decidua by BCAA and investigated its physiological effects on trophoblast cells. [Methods] Production of BP-1 by decidua was examined by immunoblot after incubation with/without BCAA. EVT migration was evaluated using the media conditioned by decidua. Phosphorylation of focal adhesion kinase (FAK) of EVT cells was also analyzed by immunoblot. The same experiments were repeated with adding RGD peptide, which inhibits BP-1 binding to $\alpha5\beta1$ integrin. [Results] EVT migration and phosphorylation of FAK was enhanced in the conditioned media, presumably due to existence of BP-1 in media. RGD treatment abrogated stimulating effects of the media on both. BCAA deprivation selectively decreased BP-1 secretion from decidua. The conditioned media deprived of BCAA had suppressive effects on EVT migration and phosphorylation of FAK. [Conclusion] We demonstrated that BP-1 directly stimulates EVT migration and that deprivation of BCAA decreased BP-1 production by decidua, thereby suppressing EVT migration, for the first time.

IS-MW-2-2 Epigenotype switch from maternal to paternal type at imprinted DMRs is associated with placental mesenchymal dysplasia

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[Objective] Placental mesenchymal dysplasia (PMD), a disorder of placental morphology characterized by placentomegaly and multicystic changes, is often associated with fetal growth restriction and death. A subset of PMDs demonstrate androgenetic/biparental mosaicism and Beckwith-Wiedemann syndrome, suggesting imprinting disruption. However, the etiology of PMD remains unknown. [Methods] We collected frozen placental tissues from 21 patients with PMD in Japan. Genetic analysis involved SNP arrays and whole-exome sequencing (WES). Epigenetic analysis consisted of bisulfite-pyrosequencing to quantitate DNA methylation of 57 imprinting-associated differentially methylated regions (DMRs). [Results] SNP array analysis showed androgenetic/biparental mosaicism in 15 PMD cases, while 6 had normal biparental inheritance. Several copy number variations (CNVs) were found, but since all have been seen in normal individuals they were unlikely to be pathogenic. WES identified no disease-associated variants. Almost all DMRs in mosaic cases had a paternal methylation pattern. In biparental cases, 19 DMRs showed aberrant methylation ; 18 had normally maternally methylated DMRs with hypomethylation, indicating a maternal-to-paternal epigenotype switch. [Conclusion] PMD may be caused not by the genetic abnormalities mentioned above, but by a maternal-to-paternal epigenotype switch at certain DMRs.