Association of Vitamin D and Its Receptor and the Severity of Ovarian Cancer

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High-grade serous ovarian carcinoma (HGSOC) and low-grade serous ovarian carcinoma (LGSOC) are the most common subhistotypes of epithelial ovarian cancer. HGSOC grows and spreads faster than LGSOC which is considered as slow-growing cancer. The 5-year survival rate of HGSOC (32.1%) is significantly lower than that of LGSOC (54.2%). Thus, efforts have been made to develop strategies for primary and adjuvant therapy relevant to HGSOC and LGSOC. Vitamin D (VD), a secosteroid hormone initially identified for its role in maintaining calcium homeostasis, exhibits pleiotropic functions. VD3 is produced in the skin upon UV-B light exposure, which is converted to 25-hydroxyvitamin D3 (25(OH)D3, the major circulating form of VD) in the liver, and then 1,25-dihydroxvitamin D3 (1,25(OH)2D3, the biologically active form of VD) in the kidneys. The active 1,25(OH)2D3 acts on VD receptor (VDR) to regulate downstream gene expression critical for cell survival, growth, proliferation, differentiation, and apoptosis. In recent years, VD has been studied as a preventive or adjuvant agent for highly prevalent cancer types. Epidemiological studies showed that VD deficiency is associated with increased mortality in breast, colon, and rectum cancer patients. VD supplementation increased 5-year survival rate of ovarian cancer patients. Therefore, experiments were designed to determine the direction action of VD on the proliferation (viability) of HGSOC and LGSOC cells. Three ovarian cancer cell lines, OVSAHO, SKOV3, and VOA6406, were selected for in vitro study. OVSAHO is an established human ovarian carcinoma cell line typically used as a reproducible in vitro source for HGSOC, whereas VOA6406 is a typical LGSOC cell line. SKOV3 is a widely used ovarian cancer cell line. Although SKOV3 cells are not considered as HGSOC or LGSOC cells, they have a high growth rate and form spheroids in culture which are similar to OVSAHO cell behaviors. All three cell lines were cultured in a mixture of RPMI1640/MCDB105/Medium199/DMEM (1:1:1:1) containing 10% (v/v) FBS, 10,000 IU/ml penicillin, 10,000 IU/ml streptomycin, 1 × MEM non-essential amino acids, and 2 mM L-glutamine at 37 °C and 5% CO_2. Treatment groups included 1,25(OH)2D3 supplementation at 0 (control), 1, 5, 10, 50 nM for 72 hours. Immunofluorescent staining was performed to detect VDR expression in cultured cells. VDR protein levels were measured by western blot. Cell proliferation (viability) was assessed using CellTiter-Glo 2.0 Cell Viability Assay. VDR expression was observed in all three ovarian cancer cell lines with intensive staining located in the nucleus. VDR levels were significantly higher in VOA6406 cells than those of SKOV3 and OVSAHO cells. The 1,25(OH)2D3 supplementation significantly decreased cell proliferation (viability) of OVSAHO, SKOV3, and VOA6406 at 50, 5, and 1 nM, respectively. The results suggest that VD can elicit direct action on ovarian cancer cells via VDR. VD supplementation inhibits ovarian cancer cell proliferation in vitro in a dose-dependent manner. Cells with low levels of VDR expression require a high dose of VD to induce inhibitory effects. For the first time, it is revealed that HGSOC and LGSOC cells exhibit different dose-response patterns to VD treatment due to differences in VDR levels. Our data support the potential of VD as adjuvant therapy for HGSOC and LGSOC. High-dose VD treatment may be required to effectively inhibit HGSOC development. Further studies are needed to delineate the underlying mechanism of VD in regulating ovarian cancer cell proliferation.