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Melatonin enhances chemosensitivity of human endothelial and breast cancer cells by regulating genes involved in angiogenesis

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Endothelial cells represent one of the critical cellular elements in tumor microenvironment playing a crucial role in the growth and progression of cancer through controlling angiogenesis. Enhancing the chemosensitivity of cancer cells is one of the most important goals in clinical chemotherapy. Melatonin exerts oncostatic activity in breast cancer through antiangiogenic actions. Vascular endothelial growth factor (VEGF) produced from tumor cells is essential for the expansion of breast cancer. The angiopoietin/Tie-2 family play an important role in regulating vessel stability. Several studies emphasize the complementary and coordinated roles of angiopoietin-2 and VEGF during angiogenesis. Thus, the aim of the present study was to investigate whether melatonin sensitizes endothelial cells to chemotherapy by regulating angiogenesis. To accomplish this we used human umbilical vein endothelial cells (HUVEC) or cocultures of HUVEC cells with MCF-7 cells. Cell proliferation was measured by the MTT method. We selected different genes which were modulated by melatonin from an array of genes involved with the process of angiogenesis. Their expression was analyzed by RT-PCR. The migration of HUVECs was measured by the Wound Healing Assay and tubulogenesis studies were performed in a tubulogenesis multiplate system *in vitro*. Only the presence of malignant epithelial cells in the cocultures altered proliferation, and stimulated ANG-1, ANG-2 and VEGF expression and decreased Tie2 expression in endothelial cells. Melatonin 1 mM added to the coculture counteracted this effect and reduced Ang-1, Ang-2 and VEGF expression and increased Tie-2 expression. In addition, vinorelbine and docetaxel decreased cell proliferation and melatonin led to a significantly greater decrease. Furthermore, it is important to point out that chemotherapy increases the expression of genes involved in angiogenesis such as *VEGF*, *ANG1*, *ANG2*, *FGFR3*, *NOS3* or *MMP14*, and melatonin pretreatment 1 mM led to a significantly decrease. Furthermore, the migration of endothelial cells and the tube formation were reduced with the chemotherapy and melatonin pretreatment resulted in a significantly higher reduction. All these results suggest that melatonin could exert a cooperative enhancement of chemosensitivity associated with the modulation of angiogenesis. Therefore, melatonin could represent a new and promising therapeutic approach to the treatment of breast cancer.

Biography

Alicia González González is a PhD student from Cantabria University School of Medicine. Currently, she is involved in Breast Cancer research and Melatonin, specifically in the sensitizing effects of melatonin to chemotherapy and radiotherapy for its antiangiogenic and antiadipogenic actions. She has published three papers and she has presented her work in five international conferences.

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