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"EFECTOS ANTINEOPLÁSICOS DE NUEVOS ANÁLOGOS DEL 1α,25(OH)$_2$-VITAMINA D$_3$"

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RESUMEN

A pesar de los grandes avances logrados en el tratamiento de las enfermedades oncológicas, la sobrevida de los pacientes se ha alargado mínimamente en algunos tipos de cáncer. Por ello resulta fundamental profundizar la búsqueda de terapias novedosas evaluando nuevos compuestos. El 1α,25$(OH)_2$-vitamina D_3 o calcitriol tiene efectos antitumorales en varios tipos de cáncer y algunos ensayos clínicos realizados han dado resultados alentadores, aunque en la mayoría de los casos se ha observado hipercalcemia, lo que dificulta la administración de la dosis necesaria para inducir una respuesta antitumoral. Por ello se han sintetizado análogos con el objeto de hallar algunos que conserven o incrementen los efectos antitumorales pero carezcan de la actividad calcémica. En este sentido, análogos de la vitamina D_3 que poseen un grupo fosfonato en su cadena lateral y los derivados de la vitamina D_2 han mostrado tener baja actividad calcémica, y los llamados tipo gemini han mostrado poseer una potente actividad antitumoral. Es por ello que en colaboración con dos grupos de investigación de Química Orgánica, hemos diseñado y sintetizado análogos de la vitamina D con estas características. En este trabajo de tesis nos propusimos evaluar la actividad calcemiante y antitumoral de tres de los análogos sintetizados. Se demostró que dos de ellos (C10 y UVB1) no poseen efectos hipercalcemiantes, mientras que el tercero (UVB2) genera hipercalcemia. Se comprobó que los dos primeros análogos poseen efectos sobre la viabilidad celular de varias líneas celulares tumorales diferentes, indicando su potencial utilidad como agentes terapéuticos. El C10 demostró ejercer los efectos anti-proliferativos más potentes y se eligió para seguir evaluando con mayor profundidad. El análisis de los mecanismos subyacentes a la actividad antitumoral demostró que el aumento en los niveles del inhibidor del ciclo celular p27 es un evento común en todos los tipos celulares estudiados. Además, se demostró que el C10 induce arresto del ciclo celular en la línea de glioma T98G, aumentando los niveles de expresión de p21 y disminuyendo los de Ciclina D1. También se identificaron algunas vías implicadas en la acción del C10. Posteriormente, se realizaron ensayos *in vivo* en modelos animales de cáncer. La administración

del C10 a un modelo animal de glioma mostró tener efectos *in vivo* disminuyendo la carga tumoral. Un ensayo similar realizado en un modelo de cáncer mamario demostró efectos inhibitorios del C10 en el proceso de metástasis. En dos modelos animales de carcinoma celular escamoso, en cambio, no se observaron efectos antitumorales. Los resultados obtenidos en esta tesis aportan evidencia que indica que este nuevo análogo podría ser, solo o en combinación con otros tratamientos, un posible agente terapéutico contra el cáncer. El calcitriol y sus análogos usualmente requieren del receptor de vitamina D (VDR) para ejercer su accion antitumoral. Teniendo en cuenta los resultados obtenidos para el C10 en gliomas y sabiendo que, hasta el momento, no se ha reportado la expresión de VDR en éstos, nos propusimos también estudiar la expresión y el rol de este receptor en gliomas humanos. Encontramos principalmente que la expresión de VDR se correlaciona con una sobrevida global más larga de los pacientes de glioblastoma multiforme. Modulando genética y farmacológicamente al VDR en una línea celular de glioma humano demostramos que este receptor se encuentra implicado en la viabilidad y la migración celular y que es necesario para los efectos del calcitriol sobre la migración celular. Estos resultados indican que el estudio de la expresión de VDR en biopsias de gliomas constituye un importante requisito para la potencial utilización del calcitriol y/o sus análogos en el tratamiento de esta entidad tumoral.

ABSTRACT

Despite major advances in the treatment of oncological diseases, patient survival has only improved minimally for some types of cancer. It is therefore vital to search new therapies by evaluating novel compounds. The 1α,25$(OH)_2$ vitamin D_3 or calcitriol has antitumor effects in several types of cancer and some clinical trials have yielded encouraging results, although in most cases side effects such as hypercalcemia have been observed. These side effects preclude the administration of the dose required to induce an antitumor response. For this reason, new analogs are being synthesized with the object of finding those that maintain or increase the antitumor effects but lack calcemic activity. In this regard, analogs of vitamin D_3 that possess a phosphonate group in its side chain and analogs derived from vitamin D_2 have shown to display low calcemic activity, and the Gemini family analogues have been shown to display potent antitumor activity. That is why, in collaboration with two research groups of Organic Chemistry, we have designed and synthesized analogues of vitamin D with these features. In this thesis work we assessed the calcemic and the antitumor activity of three of the analogues synthesized. Of the three analogues studied, two showed no hypercalcemic effects (C10 and UVB1) while the third (UVB2) induced an important hypercalcemia. The two non-calcemic analogues evidenced effects on cell viability in various cancer cell lines, indicating their potential utility as therapeutic agents. The C10 is the one that proved to display the most potent antiproliferative effects on cell lines and it was chosen to perform additional studies. The analysis of the mechanisms underlying the antitumor activity of C10 showed that the increase in the levels of the cell cycle inhibitor p27 is a common event in all cell types studied. In addition, this compound induces cell cycle arrest in the glioma cell line T98G, increasing the levels of expression of p21 and decreasing Cyclin D1. *In vivo* assays using animal models of cancer were further performed. The administration of C10 to an animal model of glioma evidenced a decrease in the tumor load. A similar experiment carried out in an animal model of breast cancer showed that C10 exerted inhibitory effects of the metastasic process. In two models of squamous cell carcinoma, in contrast, no antitumor effects were observed for C10. The

results obtained provide evidence that indicates that this new analog could be, alone or in combination with other treatments, a therapeutic agent against cancer. Calcitriol and its analogs exert their antitumor effect mainly through vitamin D receptor (VDR) action. Taking into account the interesting results obtained for C10 in gliomas and knowing that so far there have been no reported studies that describe the expression of VDR in gliomas, we proposed to investigate the expression of this receptor in human gliomas. We found that the expression of VDR correlates with a longer overall survival time of glioblastoma multiforme patients. By modulating genetically and pharmacologically VDR in a glioma cell line we showed that the receptor is involved in the cellular survival and migration processes and that is necessary for calcitriol-mediated inhibition of cell migration. The results obtained in human gliomas provide evidence that indicates that the study of the expression of VDR is an important requisite for the utilization of 1α,25$(OH)_2$-vitamin D_3 or its analogues in the treatment of gliomas.

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PUBLICACIONES Y PRESENTACIONES A CONGRESOS

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Publicaciones de este trabajo de tesis

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Salomón D.G., Grioli S.M., Buschiazzo M., Mascaró E., Vitale C., Radivoy G., Pérez M., Fall Y., Mesri E.A., Curino A.C., Facchinetti M.M. (2011). Novel Alkynylphosphonate Analogue of 1α, 25-Dihydroxyvitamin D3 with Potent Antiproliferative Effects in Cancer Cells and Lack of Calcemic Activity. *ACS Medicinal Chemistry Letters.* 2 (7); 503–508.

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Gandini N.A., Fermento M.E., Salomón D.G., Blasco J., Patel V., Gutkind S., Ryscavage A., Facchinetti M.M., Curino A.C. (2012). Nuclear Heme oxygenase-1 is associated to tumor progression in Human Head and Neck Carcinoma. *Experimental and Molecular Pathology*. 93; 237-245.

Presentaciones a congresos Internacionales

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Presentaciones a congresos Nacionales

Salomón Débora G, Ferronato María J, Fermento María E, Alonso Eliana N, Obiol Diego J, Mascaró Evangelina, Vitale Cristian, Fall Yagamare, Curino Alejandro C, Facchinetti María M. Estudios preclínicos del nuevo análogo de calcitriol C10. LVIII Reunión Científica Anual de la Sociedad Argentina de Investigación Clínica (SAIC). Mar del Plata, Buenos Aires, Arg., 21 al 23 de Noviembre 2013. Publicado ISSN 0025.7680.

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