Author's response to reviews

Title: Transcriptional effects of 1,25 dihydroxyvitamin D3 physiological and supra-physiological concentrations in breast cancer organotypic culture

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Prof. Carlos Caldas
Section Editor
BMC Cancer

Dear Prof. Caldas

We are sending our manuscript entitled “Transcriptional effects of 1,25 dihydroxyvitamin D3 physiological and supra-physiological concentrations in breast cancer organotypic culture” by Cintia Milani, Maria Lucia Hirata Katayama, Eduardo Carneiro de Lyra, JoEllen Welsh, Laura Tojeiro Campos, M. Mitzi Brentani, Maria do Socorro Maciel, Rosimeire Aparecida Roela, Paulo Roberto del Valle, João Carlos Sampaio Goes, and Maria Aparecida Azevedo Koike Folgueira, to be considered for publication in BMC Cancer, as research paper. This work has not been, and will not be, submitted for publication elsewhere until the journal has reached a decision on whether to publish the paper.

Vitamin D may have anti-tumorigenic actions by influencing the gene expression profile of target tissues, which possess vitamin D receptors. However, these effects were largely demonstrated in cancer cell lines exposed to supra-physiological concentrations of the hormone, which may not totally translate the in vivo actions of the hormone. We established a more physiological
in vitro model, represented by short term culture of breast cancer tissue slices, which maintains the epithelial mesenchymal relationships and used this organotypic culture system to elucidate the transcriptional effects of 1,25(OH)2D3 0.5nM, a near physiological concentration, which can be safely attained in vivo. Our results indicate that a short exposure to a physiological concentration of calcitriol may activate the hormone pathway, detected through an induction of expression of the target gene CYP24A1. Although there was trend towards an enriched expression of genes presenting binding sites for Vitamin D receptor, only a few genes were significantly modulated. After evaluating the hormone effects in tumor slices, we compared the effects of 0.5nM 1,25(OH)2D3 in defined populations of cancer associated fibroblasts and mammary epithelial cells. This data indicated that CYP24A1 was induced in both fibroblasts and epithelial cells and even though CD14, CA2, and IL1RL1 were primarily induced in epithelial cells there was also a trend towards up-regulation of CA2, DPP4 and IL1RL1 in cancer associated fibroblasts. In conclusion, our data indicates that short (24h) exposure to concentrations of 1,25(OH)2D3 within the physiological range, exerts modest transcriptional effects. In addition, in breast cancer samples, both epithelial cells and fibroblasts may be targets of 1,25(OH)2D3 effects.

We are also submitting another manuscript entitled “Calcitriol supplementation effects on Ki67 expression and transcriptional profile of breast cancer specimens from post-menopausal patients” to be considered for publication in BMC cancer. Both manuscripts suggest that calcitriol in a physiological concentration range has are very modest transcriptional activity.

We look forward to hearing from you

Sincerely yours

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