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The Anti-Tumor Effect of a Novel Adenosine Receptor Type A3 Agonist, LJ540, in Human Breast Cancer Both In Vitro and In Vivo

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A3 adenosine receptor (A3AR) agonists are known to inhibit the growth of various tumor cell types. The present study demonstrates that a novel A3AR agonist, LJ540, inhibited the growth of human breast cancer both in vitro and in vivo. The effect of LJ540 was investigated in various human breast cancer cell lines, MCF7, T47D (ER-positive cell lines), MDA-MB-231 and SK-BR-3 (ER-negative cell lines). LJ540 exerted the growth inhibitory effect in all four breast cancer cell lines regardless of the ER status in both dose- and time-dependent manner using MTT assay. Such inhibitory effect of LJ540 was partially due to enhanced apoptosis from the results that treated cells not only accumulated in sub-G1 phase analyzed by flow cytometry, but also resulted in nuclear fragmentation by DAPI-staining. Consistent with the apoptotic effect of LJ540, proteolytic cleavages of Caspase-3 and PARP were observed in both ER-positive and -negative breast cell lines. Furthermore, LJ540 induced the down-regulation of the canonical Wnt signaling pathway as seen by increased GSK-3β expression and reduced Cyclin D1 expression. Finally, we performed oral administration of LJ540 for 1 month in a xenograft model using nude mice bearing T47D and MDA-MB-231 cells to clarify the anti-tumor effect of LJ 450 in vivo. Interestingly, LJ450 significantly reduced tumor size in both ER-positive and -negative breast cancers. Taken together, the A3AR agonist LJ540 exhibited anti-tumor effect regardless of the ER status both in vitro and in vivo, and involved the activation of the pro-apoptotic proteases and the down-regulation of the canonical Wnt signaling pathway.

Keyword: A3 agonist, breast cancer, Wnt signaling pathway, apoptosis