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Cannabinoids increase lung cancer cell lysis by lymphokine-activated killer cells via upregulation of ICAM-1.

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Author information**Abstract**

Cannabinoids have been shown to promote the expression of the intercellular adhesion molecule 1 (ICAM-1) on lung cancer cells as part of their anti-invasive and antimetastatic action. Using lung cancer cell lines (A549, H460) and metastatic cells derived from a lung cancer patient, the present study addressed the impact of cannabinoid-induced ICAM-1 on cancer cell adhesion to lymphokine-activated killer (LAK) cells and LAK cell-mediated cytotoxicity. Cannabidiol (CBD), a non-psychoactive cannabinoid, enhanced the susceptibility of cancer cells to adhere to and subsequently be lysed by LAK cells, with both effects being reversed by a neutralizing ICAM-1 antibody. Increased cancer cell lysis by CBD was likewise abrogated when CBD-induced ICAM-1 expression was blocked by specific siRNA or by antagonists to cannabinoid receptors (CB1, CB2) and to transient receptor potential vanilloid 1. In addition, enhanced killing of CBD-treated cancer cells was reversed by preincubation of LAK cells with an antibody to lymphocyte function associated antigen-1 (LFA-1) suggesting intercellular ICAM-1/LFA-1 crosslink as crucial event within this process. ICAM-1-dependent pro-killing effects were further confirmed for the phytocannabinoid $\Delta(9)$ -tetrahydrocannabinol (THC) and R(+)-methanandamide (MA), a hydrolysis-stable endocannabinoid analogue. Finally, each cannabinoid elicited no significant increase of LAK cell-mediated lysis of non-tumor bronchial epithelial cells, BEAS-2B, associated with a far less pronounced (CBD, THC) or absent (MA) ICAM-1 induction as compared to cancer cells. Altogether, our data demonstrate cannabinoid-induced upregulation of ICAM-1 on lung cancer cells to be responsible for increased cancer cell lysis by LAK cells. These findings provide proof for a novel antitumorigenic mechanism of cannabinoids.

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