TRPV1 modulation of immune response in metastatic breast carcinoma: Enhanced inflammatory response may hinder therapeutic potentials of TRPV1 agonists

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Abstract

Background and Purpose: The transient receptor potential vanilloid 1 (TRPV1) ion channels enhance cytotoxic immune response and may have therapeutic potential in cancer treatment. Hence, we here determined how activation of TRPV1 alters immune response of tumor-bearing mice. Experimental Approach: Three different metastatic subset of 4T1 breast carcinoma cells were used to induce tumors in Balb-c mice. Mix leukocyte cultures (MLCs) using spleens and draining lymph nodes were prepared and stimulated with various challenges. Effects of four different TRPV1 agonists, antagonist (AMG9810) and Gambogic Amide (GA), a TrkA agonist that sensitizes TRPV1, on secreted levels of cytokines were determined. Results: MLCs of tumor-bearing mice secreted markedly higher levels of IL-6 and lower levels of IFN-γ compared to control mice. We observed differential effects of TRPV1 agonists, antagonist and GA in control and mice bearing different subset of metastatic cells. TRPV1 and TrkA agonists increased IFN–γ and IL-17 secretion in control mice while they markedly increased IL-6 secretion and suppressed IFN–γ secretion in tumor-bearing mice. Unexpectedly, AMG9810 acted as an inverse agonist and did not antagonize the effects of TRPV1 agonists and GA did not sensitize TRPV1 channels. Conclusions: Our results demonstrate constitutive activity of TRPV1 in immune cells, suggesting cross activation. Excessive chronic activation of TRPV1 in immune cells in the presence of metastatic breast carcinoma may have detrimental effects. Unexpected findings further document that a drug can have multiple intrinsic activities and depending on surrounding factors can act on the same receptor as an agonist, antagonist or inverse agonist.

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