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HuAL1 peptide from complementarity-determining region 1 (CDR-1) of mAb HuA induces necroptosis in B16F10-Nex2 cells

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Treatment of melanoma, mainly on the metastatic stage, is a great clinical challenge because conventional chemotherapy is rather ineffective. Other strategies, including immunotherapy, have been introduced and are very encouraging. We have previously shown that peptides derived from complementarity determining regions of immunoglobulins (CDRs) display antimicrobial and antitumor activities regardless of the specificity of the antibodies they were derived from. In the present study, we show that CDR 1 from the light chain (L1) of a human IgM, mAb (HuA), specific for difucosyl human blood group A (HuA) induces necroptotic cell death in the murine melanoma cell line B16F10-Nex2 and in other murine and human tumor cell lines. HuAL1 did not exert cytotoxic effects in non-tumorigenic cell lines. Melanoma cells treated with HuAL1 showed DNA degradation, propidium iodide incorporation and abundant superoxide anion production. Moreover, peptide treatment induced mitochondrial swelling and disruption of mitochondrial cristae. All these effects were caspase-independent and RIPK1- and MLKL-dependent, since cell death was abolished when cells were co-incubated with necrostatin or necrosulfonamide. Confocal microscopy showed that HuAL1 peptide localizes to the cell nucleus, and ELISA assay showed that it probably binds to H3 histone. We propose that necroptosis is induced after chromatin disorganization upon peptide binding to histone. Our results show, for the first time, that a peptide derived from an Ig-CDR can induce necroptotic cell death on tumor cells.

Biography

Denise C Arruda is graduated in Pharmacy from the Federal University of Santa Catarina in 2000. She pursued PhD in Biology Sciences from University of São Paulo (ICB-USP) with postdoctoral degree at the Experimental Oncology Unit - Discipline of Cell Biology, Federal University of São Paulo from 2008-2014. Currently, she is a professor and researcher at the Integrated Nucleus of Biotechnology at University of Mogi das Cruzes. She has published 17 papers in reputed journals, some of them in collaboration with international research groups, and received awards for poster presentation in five international meetings.

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