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Peptide R18H from Brn-2 transcription factor POU domain displays anti-melanoma activity *in vitro* and *in vivo*

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The Brn-2 transcription factor is related to the development of malignant melanoma, inducing cell proliferation and invasion and, consequently, the formation of metastases. The Brn-2 protein is expressed in melanocytes and overexpressed in melanoma cells. Peptides derived from the Brn-2 transcription factor could compete with the DNA binding sites, thus interfering with the development of melanoma, as well as activating the mechanisms of cell death. In the present work, the cytotoxic activities of peptides derived from the Brn-2 transcription factor were determined against murine melanoma B16F10-Nex2. Cells were treated for 24h with the peptides E12F, R18H, L13S and C9K, derived from the POU domain of the Brn-2 transcription factor. Among the peptides tested, only the R18H peptide was cytotoxic in B16F10-Nex2 cells. Moreover, a time curve was taken to evaluate the antitumor activity of R18H for 30 minutes, 1, 2, 4, 6, 12 and 24 hours. It was observed that the peptide displays antitumor activity early in the first hours of treatment, however, the cytotoxic effect increases only after 24 hours. The R18H peptide induced DNA degradation, chromatin condensation, increase of superoxide anions, phosphatidylserine translocation, activation of caspase 3 and 8, and release of extracellular cytochrome c in B16F10-Nex2 cells. These effects characterize death by apoptosis and because caspase 8 was activated we suggest that the extrinsic pathway is followed. R18H also induced membrane permeabilization in cells treated for 24 h, however, the same effect was not observed after treatment for 2 h. To determine if the membrane permeabilization effect could be due to late apoptosis or if in addition to apoptosis the R18H peptide also induced necrosis or necroptosis, we tested the peptide in the presence of necroptosis inhibitors and verified the release of LDH in the extracellular environment of treated cells. The peptide kept its cytotoxic effect in the presence of inhibitors of necroptosis and treated cells did not present LDH release in the extracellular medium. These data indicate that membrane permeability is a late apoptosis event. It was also observed that peptide R18H showed antitumor activity *in vivo*. It was observed in the metastatic model that C57Bl/6 mice treated with the R18H peptide showed lower numbers of pulmonary nodules than untreated mice. The peptide was not toxic in mice at high doses, as observed in histopathological analysis of the lung, liver, kidney, heart and spleen. These results suggest that the R18H peptide has potential to be developed as a new drug for the treatment of melanoma.

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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