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FoxM1 transcription factor as a potential target for therapeutic intervention in breast cancer

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Abstract

Resistance to therapy is the main cause of treatment failure in breast cancer, despite recent advances in treatment in the last decades. Increasing evidence show that Survivin and XIAP antiapoptotic proteins and FoxM1 transcription factor overexpression are closely associated with poor prognosis in breast cancer. In this study, we explored the role of FoxM1 in drug resistance as well as in the regulation of Survivin and XIAP. Using breast cancer cell lines, we observed that doxorubicin inhibited cell viability and induced DNA fragmentation and caspase activation, following a reduction in Survivin and XIAP protein and mRNA levels. However, Survivin-induced overexpression did not result in a cell death-resistant phenotype. Accordingly, XIAP and Survivin silencing through siRNA, individually or in combination, had little effect on breast cancer cells sensitivity towards doxorubicin, indicating that the drug can induce cell death regardless of their expression. In order to understand mechanisms underlying Survivin and XIAP drug-mediated downregulation, we transfected cells with a FoxM1-encoding plasmid and observed that Survivin and XIAP are upregulated at both protein and mRNA levels. Importantly, FoxM1-overexpressing cells had caspase activation and DNA fragmentation levels attenuated after exposure to both doxorubicin and docetaxel. These results demonstrate that FoxM1 might cooperate with Survivin and XIAP antiapoptotic proteins to promote resistance to docetaxel and doxorubicin. Altogether, our data point FoxM1 transcription factor as an interesting novel therapeutic target for future interventions and suggest that combining FoxM1 inhibitors with conventional chemotherapy has the potential to circumvent resistance in breast cancer.

Biography

Gabriela Nestal de Moraes has completed his Ph.D at the age of 27 years from Brazilian National Cancer Institute, where she is taking her postdoctoral studies. She has been dedicating her studies to understanding molecular mechanisms underlying drug resistance in cancer, especially in leukemia and breast cancer.