Cardiac glycosides exert anticancer effects by inducing immunogenic cell death.


Source

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Abstract

Some successful chemotherapeutics, notably anthracyclines and oxaliplatin, induce a type of cell stress and death that is immunogenic, hence converting the patient's dying cancer cells into a vaccine that stimulates antitumor immune responses. By means of a fluorescence microscopy platform that allows for the automated detection of the biochemical hallmarks of such a peculiar cell death modality, we identified cardiac glycosides (CGs) as exceptionally efficient inducers of immunogenic cell death, an effect that was associated with the inhibition of the plasma membrane Na(+) and K(+) dependent adenosine triphosphatase (Na(+)K(+)ATPase). CGs exacerbated the antineoplastic effects of DNA-damaging agents in immunocompetent but not immunodeficient mice. Moreover, cancer cells succumbing to a combination of chemotherapy plus CGs could vaccinate syngeneic mice against a subsequent challenge with living cells of the same type. Finally, retrospective clinical analyses revealed that the administration of the CG digoxin during chemotherapy had a positive impact on overall survival in cohorts of breast, colorectal, head and neck, and hepatocellular carcinoma patients, especially when they were treated with agents other than anthracyclines and oxaliplatin.

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