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Advances on photodynamic therapy through new pyridine-fused diphenylchlorins as photosensitizers for melanoma treatment

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Aim: Assessment of cytotoxicity of four new photosensitizers intended for photodynamic therapy (PDT) against melanoma cells (A375 cells).

Introduction: Melanoma is the rarest form of skin cancer. PDT combines a photosensitizer with light culminating in the production of reactive oxygen species leading to cellular death. A new type of stable 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-fused tetraphenylchlorins1, proved to be very active as photodynamic agents. Thus, looking for a new generation photosensitizers with optimized properties for PDT we synthesized new diphenylchlorins.

Methods: The human melanoma cell line A375 was seeded in 48 well plates. The photosensitizers NAMP103A, NAMP103B (the tetraphenylchlorins monoester), NAMP263A and NAMP263B (the tetraphenylchlorins alcohol) were administered ranging 5 nM to 10 μM. Irradiation was performed after 24 h (λ < 560 nm). MTT and SRB assays as well as flow-cytometry were performed 24 h after the PDT.

Results: MTT assay results allowed to obtain dose-response curves and to calculate the concentration that inhibits the cultures by 50% (IC50). Phototoxicity (10J) was dependent on the chlorines concentration. Moreover, NAMP263B was significantly more cytotoxic than NAMP103A (p = 0.037) and NAMP103B (p = 0.042). From SRB assay we verified that with a 125 nM concentration the NAMP103A, NAMP103B, NAMP263A and NAMP263B produce a cellular viability of 36.9%; 33.2%; 18.3% and 18.8%, respectively. Flow cytometry studies confirmed the decrease of viability associated with cell death by apoptosis and necrosis. Loss of mitochondrial membrane potential, apoptosis hallmark, was also observed. An imbalance of ROS, namely superoxide anion and peroxides, was observed for all photosensitizers studied with an exhaustion of antioxidative intracellular defenses (GSH).

At low PS concentrations (5 nM), metabolic activity was variable with light energy (5 J, 10 J and 20 J) with lower values for higher fluence. Dark toxicity studies revealed photosensitizer dependence of irradiation.

Conclusion: We hereby conclude that the photosensitizers are indeed very promising, which rouses plans for following proceedings to verify in vivo outcome.

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References

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Angiogenesis and inflammation at the crossroads between diabetes and cancer

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Aim: To study fibrosis, angiogenesis, oxidative stress and inflammation markers in diabetic and non-diabetic patients with gastric cancer (GC).

Introduction: Type 2 Diabetes mellitus (DM2) is a major health problem, with 415 million people diagnosed worldwide. Evidence regarding its association with various types of cancer has been reported, including GC. Some hypotheses have been suggested to explain how DM2 could enhance the risk of cancer development, such as hyperglycemia, hyperinsulinemia, oxidative stress, vascular disturbances and a chronic low inflammation state.

Gastric cancer (GC) is the fifth most common cancer worldwide and ranks as the third leading cause of cancer-related death. GC is frequently associated with infection by Helicobacter pylori and inflammation plays a central role in the carcinogenic process. Such chronic inflammatory state, linked with angiogenesis imbalance, oxidative stress and metabolic signaling, suggests that also DM2 might be a major risk factor in initiation and progression of GC, demanding further investigation.

Methods: A series of GC from DM2 (n = 22) and nonDM2 (n = 21) patients were studied. Immunohistochemistry (IHC) using antibodies against CD31 and 3-Nitrotyrosine was performed, to assess density of vessels and oxidative stress status. Histochemical staining with Sirius red was performed to determine the percentage of fibrosis in the tumor and non-neoplastic adjacent mucosa. Based on assessment of tumor inflammatory cell infiltrate and tumor stroma...
Circulating EVs for AML minimal residual disease biomarkers detection

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Abstract: EVs potentially carry molecular signatures associated with specific cancer phenotypes. Here, we report the profile of exosomal proteins isolated from AML patients' blood plasma. The EV profile showed a significant shift in the expression of some proteins, compared to healthy controls, suggesting that EVs could be a promising source of biomarkers for AML monitoring.

Introduction: AML is a hematopoietic stem cell disorder with high mortality rate mainly due to the high frequency of post-treatment relapse. Minimal residual disease (MRD) determination in AML patients receiving treatment is useful to assess chemotherapy response and predict relapse. One approach to upgrade the current invasive MRD monitoring (traditionally based on bone marrow aspirates/biopsies) is to use non-invasive methods that identify cancer-associated biomarkers in patients' blood. The method of the study monitored the profile of EVs isolated from AML patients' blood, and compared the EV composition between healthy controls and AML patients.

Methods: AML patients and healthy controls were enrolled in this study. Exosomes were isolated from blood samples using size-exclusion chromatography. The EV profile was analyzed using mass spectrometry and Western blotting. The results showed a significant shift in the expression of some exosomal proteins in AML patients, compared to healthy controls, suggesting that EVs could be a promising source of biomarkers for AML monitoring.

Results: EVs with decreasing size were successfully isolated between SEC fractions 3 to 6, with a size ranging from 300 nm to 10 nm, respectively. Fraction 2 presented the smaller EVs, although mixed with smaller EV subpopulations between fractions 3 to 7. The expression of leukemia-specific markers is currently being studied in the EVs isolated from the paired AML blood samples.

Conclusion: The presented EV-based liquid biopsy method would contribute to improve the current invasive MRD monitoring. AML monitoring could unravel biomarkers for diagnostic and prognostic purposes in AML patients.

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The association of Generalized Epilepsy with Febrile Seizures plus (GEFS+) with FEB1 gene: A new insight to the etiology of GEFS+

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