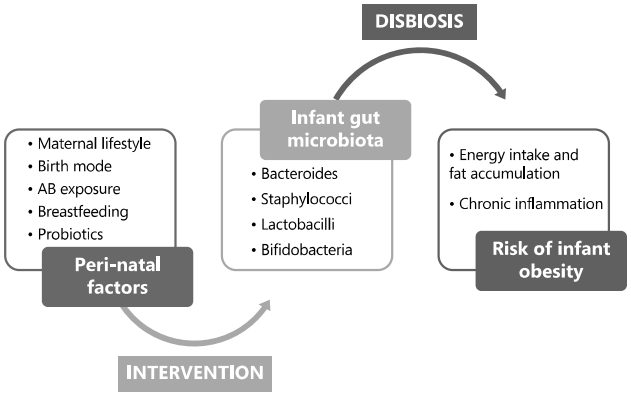
Conclusions:



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11 – Differential Imune Response to Vitamin A in B16-F10 Malignant Melanocytes

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Introduction: Melanoma is an aggressive form of skin cancer with a poor prognosis, due to its refractory behavior to radiation and chemotherapy. Although the diagnosis is straightforward, there are many disagreements regarding its treatment and surveillance. [1, 2, 3] In order to surpass some of the limitations addressed to the treatment, preventive methods like antioxidant vitamins are nowadays a relevant field of research, as well as immunostimulation by external agents. [4] Despite the knowledge about melanoma biology, pathogenesis and developed therapies, [2] is important to understand the effect of vitamin A in order to suggest alternatives to conventional therapies, [5] which are known to be ineffective against melanoma.

Objectives: The main goal of the present project was to create and develop an *in vitro* model that could be used to address the use of antioxidant vitamins as therapeutic contributors. In particular, we wanted to understand the redox effect of vitamin A in a melanoma cell line (B16-F10) as well as to understand its role in the immune system by assessing the activation of naïve macrophages (Raw 264.7).

Materials and Methods: All experiments were performed on melanoma cells, B16-F10, and macrophage-like cells, Raw 264.7. B16-F10 cells were treated with different concentrations of hydrogen peroxide (H_2O_2), different concentrations of vitamin A and with a mixture of H_2O_2 + vitamin A. Raw 264.7 cells, in co-culture with B16-F10, were also treated with different concentrations of vitamin A. The metabolic activity was measured by MTT assay.

Results and Discussion: Lower doses of vitamin A resemble an enhancement of the cytotoxic activity of macrophages, whereas higher concentrations could have the opposite effect.

Conclusion: The co-culture experiment allowed the study in a more complex environment showing that the possible therapeutic effect of vitamin A was inversely correlated to the results of melanoma cell cultures alone. However, further studies are needed in order to validate the proposed results.

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12 – Mitochondrial DNA Depletion Re-programs the Expression of Fatty Acid Metabolism-related Genes and Leads to Lipid Droplet Accumulation

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Metabolism and the Warburg effect are considered cancer hallmarks. The last few decades revealed the importance of lipid metabolism and lipid droplets (LDs) in cancer biology. Although mitochondria play a central role in overall cellular metabolism, the influence of mitochondrial dysfunction (particularly due to mitochondrial DNA (mtDNA) pathogenic mutations) in lipid metabolism and cytoplasmic LD accumulation in cancer remains unclear.

In this work, we aimed to link mitochondrial dysfunction with lipid metabolic re-programming, with focus on fatty acid (FA) metabolism. Specifically, we aimed to understand if pathogenic mutations in mtDNA lead to cytoplasmic LDs alterations (number and/or size) and to identify key genes involved in alterations of FA metabolism.

To do so, we characterized the lipidic profile of seven cybrid cell lines (osteosarcoma derived cell lines), as a model of mitochondrial dysfunction due to the presence of mtDNA alterations. Our data demonstrates that LDs content, as well as LDs number and size, are influenced by mtDNA depletion. Concomitantly, we showed that mtDNA depletion induces profound alterations in FA metabolism by altering the expression of different metabolic genes, and identified three genes potentially involved in LDs accumulation and/or lipid metabolic re-programming.

Additionally, mtDNA mutations and mutation load differently impact FA metabolism by modulating expression of genes involved in this pathway.