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Evaluation of the anticancer effect and immune cells' activation induced by HFn-mAbs treatment on 3D tumor models

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Abstract:
Cancer is a highly complex and heterogenous disease that includes different morphological features, various molecular markers and unrelated clinical behaviours. Furthermore, the enormous ability of tumors to evade therapies through defence systems make them difficult to treat. In this scenario, immunotherapy could be a promising approach to overcome the limitations of conventional therapies aiming to re-educate the host immune system to recognize the cancer cells as "non-self" and consequently react against them. Antibody-based therapy is one of the most successful strategies in use for the treatment of highly aggressive cancer subsets. Indeed, monoclonal antibodies (mAbs) have the ability to promote the tumor killing both by immune cells activation through a mechanism known as antibody-dependent cellular cytotoxicity (ADCC) and by the direct inhibition of tumor proliferation and survival pathways. However, the therapeutic efficiency of mAbs is still limited by problems related to their poor pharmacokinetics and crossing of biological barriers.
Nanoparticles proved to be a promising strategy to overcome mAbs' limitations because they can be both functionalized on the surface with specific ligands and exploited as vehicles for drugs delivery. Among them, H-ferritin (HFn), a recombinant form of human apoferritin, has been extensively studied because it is biocompatible, it can be loaded with drugs and exhibits tumor targeting by recognition of transferrin receptor 1 (TfR1), overexpressed in 98% of human cancers.
After demonstrating that HFn is an efficient carrier to enhance the blood brain barrier crossing of mAbs without the loss of their antitumoral activity on 2D tumor models, we focused on the evaluation of the activity of HFn-mAb nanoconjugates on 3D cellular models. First experiments were carried out to optimize the formation of cancer spheroids of glioblastoma and breast cancer cell lines and to evaluate the internalization of HFn-mAbs by flow cytometry and confocal microscopy. Then we investigated the ability of HFn-mAb nanoconjugates to trigger the ADCC by Operetta live imaging system monitoring over time the increase in mortality resulting from the activation of the apoptosis mechanism. To further confirm the ability of our nanoconjugates to initiate ADCC, we also studied the activation of NK cells. The data obtained so far with 3D models demonstrated the efficacy of HFn-mAbs to trigger an anticancer effect and to activate the immune system. In the future we'll try to co-administer our HFn-mAb with Doxorubicin-loaded ferritin in order to combine the immune system activation with the chemotherapeutic activity of this drug.