

Preclinical tumor organoid models in gastric cancer: the missing link for targeted therapy and personalized cancer treatment.

Neoadjuvant chemotherapy (NAC) plays an important role in the therapeutic strategy of locally advanced gastric cancer (GC). Unfortunately, the heterogeneous cellular and molecular nature of GC results in NAC resistance and subsequent loss of benefit in almost 50% of treated patients. Currently, predictive biomarkers to guide perioperative treatment drug selection, are still heterogeneous and hardly applicable to clinical practice. Therefore, it appears crucial to early understand which patients will benefit from NAC, based on reliable predictive factors, in order to personalize the therapeutic approach. It is also relevant to consider that NAC and adjuvant chemotherapy (AC) therapy are related. The aim of this project is to identify pathways and Master Regulator (MRs) associated with NAC efficiency by molecular characterization (various -omics) of patient derived GC fresh-frozen tissues (pGC). In particular, we will investigate whether those biomarkers are intrinsic to the patient or induced by NAC by exploiting the paired pre-NAC biopsies. The secondary aim of the project is to assess whether patient-derived GC organoids (GC-PDOs) are a reliable ex-vivo study model to evaluate and/or predict pharmacological response. GC-PDOs appear promising in addressing this concern. Using GC-PDOs could mimic the complexity of the in vivo situation overcoming the limitations of traditional in vitro and in vivo cancer models. GC-PDOs might enable to properly select patients who could benefit from tailored treatments, optimizing the risk/benefit ratio of chemotherapeutic regimens. Briefly, the pGC analyses may lead to the identification of altered molecular signatures involved in chemoresistance development and to improve the prognosis of patients by predicting the NAC response to therapy and the AC regimen efficacy. Moreover, our proposed GC-PDOs ex-vivo study platform will allow to efficiently test potentially targetable pathways empowering personalized medicine approaches.

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