CANCER REPOPULATION AND ACQUIRED CHEMO-RESISTANCE (CRAC) AS AN EXAMPLE OF NON-DARWINIAN TUMOR EVOLUTION

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Cancer arises from normal cells that acquire a transformed phenotype and evolves progressively increasing malignancy (cancer progression). Since the discovery of oncogene mutations, tumor progression was considered an evolutionary process responding to Darwinian rules, selecting survival and expansion of the "fittest" clones, those bearing the mutations mostly favouring proliferation, survival and motility.

It is emerging that many processes related to tumor evolution, originally attributed to the genetic diversity, are instead due to aberrant homeostasis of the cancer tissue, due to altered epigenetic patterns. This implies that the phenotypic evolution of tumors may obey to another type of evolution, rather resembling the phenotypic programmed progression occurring during organism development.

Counterintuitively, a major promoter of tumor progression is cytotoxic anticancer therapy. The aim of this therapy is the elimination of cancer killing most of cancer cells by the administration DNA damage induction agents that activate DNA damage response (DDR) and apoptotic pathways, leading cell to apoptosis. The strong cancer cells number decrease and the genomic instability generated by therapy, induce a selective pressure on cancer population preserving cells with more malignant phenotype. But genetic selection is not the only mechanism of therapy-promoted tumor progression. The fraction of cells surviving the treatment re-organize injured cancer tissue through a phenotypic evolution including epigenetic changes. This phenomenon sums up with Darwinian selection, exacerbated by the genetic instability promoted by cytotoxic therapy.

Repopulation is not a spontaneous process but is actively promoted by signals from injured tissues. Caspase-3 activation of apoptotic dying cells elicits a paracrine signal producing prostaglandin E2 (PGE2), stimulating proliferation and repopulation, which are accompanied by increase motility and chemoresistance. This clinically coincides with post-therapy relapse.

In the three years of the PhD research, we aim to study a system to control and counteract cancer repopulation looking for alternative methods to the classic cytotoxic agents that can avoid the activation of pathways essential for tumor repopulation. Thus, we will investigate the effects of non-cytotoxic modulator agents, e.g. nuclear receptors, already used on anticancer therapy as "normalizing" agents of cancer phenotype without DNA damage induction, studying their effect on therapy-acquired cancer phenotype, repopulation and therapy acquired chemoresistance, analysing DDR, apoptosis pathway and PGE2 production.