Cell plasticity is the ability of cells to shift, in a reversible manner, between distinct phenotypic and molecular states and is inherent to the development of multicellular organism. Indeed, the majority of adult tissues and organs are the result of the conversion of epithelial into mesenchymal cells through a process called Epithelial to Mesenchymal Transition (EMT), which is reversible, as well as its inverse process (MET). Cell plasticity is not confined to physiological embryonic development but it is reactivated at the onset of several pathological conditions, including tumor progression and fibrotic diseases affecting different organs including heart, lung, liver and kidney among others.

Increasing evidence point to a key role of metabolites availability in the control of cell plasticity and, in particular, in the underlying epigenetic mechanisms. Indeed, several epigenetic enzymes are sensitive to fluctuation in metabolites levels, which may in turn induce epigenetic changes associated with cell fate decisions1. In this context, we have discovered that a high Proline regimen drives embryonic stem cells (ESCs) towards a fully reversible embryonic stem-to-Mesenchymal-like Transition (esMT), which resembles the EMT that occurs during metastasis formation2,3; and that supplemental ascorbic acid (VitC) fully counteracts esMT and induces the reversed MesT4.

We thus exploited the morphological changes associated with esMT to perform a phenotype-based high-performance drug screening assay, using a library of 1200 FDA-approved drugs, which allowed us to find previously unrecognised modulators of cell plasticity.

We identified: i) 137 drugs able to fully inhibit ESC proliferation; and found that most (80%) of these compounds have anti-cancer activities, thus supporting the notion that stem and cancer cells share a similar chemo-sensitivity spectrum; and ii) 14 drugs that block esMT, without preventing cell proliferation. We thus used these drugs to investigate the molecular mechanisms underlying cell plasticity, and found that a rapid increase of Proline-dependent collagen synthesis leads to an increased activity of collagen prolyl-hydroxylase enzymes, which are involved in collagen maturation and consume Vitamin C (VitC) in the endoplasmic reticulum (ER)5. As a consequence, the nuclear availability of VitC becomes limiting for the VitC/dKG/Fe²⁺-dependent epigenetic enzymes, such as the histone (JmjC) and DNA (Tet) demethylases, leading to genome-wide increase of histone and DNA methylation6. In line with the idea that esMT resemble pathological EMT, a combined pharmacological and genetic approach allowed us to reveal that this functional interplay contributes to cancer cell plasticity and metastatic progression. In particular, we identified Budesonide, a drug commonly used to treat asthma and reduce collagen in pathological fibrotic diseases, as a potential anti-metastatic drug. Budesonide impairs the acquisition of motile/invasive features in lung and triple negative breast cancer cells, and, reduces tumor metastasis in vivo6.

We thus propose a model whereby a Proline cycle, i.e. free Proline generated by degradation of extracellular collagens, is used for intracellular collagen synthesis, and modifies the epigenetic landscape and heterogeneity of both normal stem and cancer cells7. We suggest that targeting this metabolic-epigenetic axis may pave the way in the future for the treatment of different types of metastatic cancers, as well as for developing novel therapeutic strategies for fibrotic diseases. We are combining the development of 3D organotypic cultures of embryonic stem cells (e.g. gastruloids)8 and tumor cells (cancer organoids) with a drug screening approach, with the ultimate goal to identify novel compounds able to modulate cell plasticity in physiological and pathological conditions.
References:


Keywords:
cell plasticity
cell metabolism
drug-screening

Contacts:
cristina.daniello@igb.cnr.it
eduardo.patriarca@igb.cnr.it

Website(s):

Other: