TARGETING THE CANCER RESISTOME TO RESTORE TUMOUR SENSITIVITY THROUGH NOVEL, EXISTING AND FAILED DRUGS

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In the last two decades we witnessed many progresses concerning the discovery, the development and the clinical application of anti-cancer drugs. However, old and new drugs share the common drawback of the resistance that is the major problem facing current cancer research. An initial response to treatment is often followed by disease progression, which, accompanied by a reduction of therapeutic options, ultimately leads to treatment failure and death from recurrent or metastatic disease. There is a growing body of evidence recognizing that drug resistance onset is the consequence of several processes including secondary mutations and adaptive responses resulting from genetic and epigenetic influences, such as miRNA deregulation, and tumour microenvironment (TME) control. In this context therapy-resistant cancers harbour highly complex signalling networks – the resistome – including miRNA deregulation, inflammation, angiogenesis and TME. To develop strategies to counteract drug resistance, it is essential to understand the basic molecular mechanisms through which cancer cells control drug sensitivity. In this perspective this study investigates the resistome. To pursue this objective we have generated a resistance profile, or resistome, of three tumour models, two of epithelial origin, non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), and the gastrointestinal stromal tumour (GIST), the most common mesenchymal tumour of the gastro-intestinal tract. In these models we study the cross-talk between drug resistance and inflammation, drug resistance and integrin function, and the interplay of the above with stemness and angiogenesis. An additional aim is to dissect how cell-autonomous cancer phenotypes, angiogenesis and cell-extrinsic composition of the metastatic microenvironment are governed by miRNA regulatory networks. The most relevant findings on the identification of the resistance features of three tumour models of high impact and interest of this just-started project will be presented. In the CRC model in particular, the metastatic microenvironment of the liver, simulated by the association of soluble (a hepatocyte's conditioned medium) with structural (the proteins of the extracellular matrix) factors influences one of the first steps of the organ colonization, i.e. the adhesion process, of HT-29, Caco-2 and HCT-116 cells, with a more pronounced effect on this latter CRC invasive cell line (Pelillo et al., 2015).

In NSCL cancer cells resistant to Gefitininb (GR) we observed an inflammatory phenotype documented by increased expression/levels of microsomal prostaglandin E synthase-1(mPGES-1)/PGE2, mesenchymal and staminal markers. GR cells were also able to form 3D spheroids, mimicking cancer stem cells function. Inhibition of PGE2 signalling in GR cells reverted their staminal/mesenchymal phenotype.

The achievement of the final project goal will help the management of the drug resistance, providing a tool to assist clinicians in the choice of the best therapeutic combination for patient care.

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Pelillo et al, (2015). J Cell Biochem. 116, 2385-96.