The tumor microenvironment in therapy response and resistance: challenges and opportunities

Abstract

The identification of molecular drivers in cancer has paved the way for targeted therapy. However, incomplete responses and relapse on therapy remain the biggest problem for improving patient survival. Evidence suggests that a tumor consists of a majority of cells that are sensitive to targeted therapy while few cells that are intrinsically resistant or poised to quickly adapt to drug treatment already pre-exist within this heterogeneous tumor population. Although a multitude of resistance mechanisms have been described, it was largely unknown how resistant cells behave in a heterogeneous tumor during treatment and whether the microenvironment of a regressing tumor could influence disease relapse.

We found that targeted therapy with BRAF, ALK, or EGFR kinase inhibitors induces a complex network of secreted signals in drug-stressed melanoma and lung adenocarcinoma cells. This therapy-induced secretome (TIS) stimulates the outgrowth, dissemination, and metastasis of drug-resistant cancer cell clones in the heterogeneous tumors and supports the survival of drug-sensitive cancer cells, contributing to incomplete tumour regression. The vemurafenib reactive secretome in melanoma is driven by down-regulation of the transcription factor FRA1. In situ transcriptome analysis of drug-resistant melanoma cells responding to the regressing tumour microenvironment revealed hyperactivation of multiple signalling pathways, most prominently the AKT pathway. Dual inhibition of RAF and PI3K/AKT/mTOR pathways blunted the outgrowth of the drug-resistant cell population in BRAF mutant melanoma tumours, suggesting this combination therapy as a strategy against tumour relapse. Thus, therapeutic inhibition of oncogenic drivers induces vast secretome changes in drug-sensitive cancer cells, paradoxically establishing a tumour microenvironment that supports the expansion of drug-resistant clones but is susceptible to combination therapy. Finally, I will discuss how a better understanding of the therapy-induced alterations in the tumor microenvironment could open up new possibilities for potent therapeutic combinations, including combinations with immunotherapies.

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Room A204 - Polo Ferrari 1
via Sommarive 9, Povo (TN)