The road to studying the impact of matrix stiffness to lung cancer cell treatment response

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ABSTRACT

Lung cancer is the leading cause of morbidity and mortality worldwide. Unfortunately, most lung cancers present as stage IV attributed to metastatic disease, which is associated with increased symptom burden and poor survival. Novel and potent therapy options, including EGFR inhibitors such as Osimertinib, have transformed the treatment of some subsets of lung cancer; nevertheless, the clinical benefit is still limited to a minority of patients reflecting the need to better understand the underlying biology of the disease. Lung cancer can start in any part of the lungs or airways. Thus, tumors from different patients are expected to grow in microenvironments with distinct extracellular matrix (ECM) characteristics. Stiffness is a biophysical property of the matrix associated with tumor cell proliferation, metastasis, dormancy and chemoresistance. While it is well established that stiffness influences the behavior of normal cells, the role of matrix stiffness in transformed cells is not as clear.

Currently, in the lab, we aim to understand how extracellular matrix stiffness regulates the growth and migration potential of EGFR-driven lung cancer cells, as well as to explore the impact of stiffness to their response to treatment and the development of drug resistance.

Here, we used four EGFR-driven lung cancer cell lines (PC-9, HCC-827, NCI-H2279 and HCC-4006) and fabricated thin polyacrylamide (PA) hydrogels with tunable stiffness levels mimicking soft or stiff matrix as we have published previously (Barber, Georgiadou et al JSC 2020).

We found that all four cell lines respond to stiffness with the cells appearing smaller, rounder and with less protrusions on soft compared to stiff matrix. In addition, the cells grow slower on soft matrix. Interestingly, the cell lines present a heterogenous phenotype in regards to their migratory behaviour. Some move faster on stiff and exhibit durotaxis (HCC827 cells) – directionality towards stiffer environment-, similar to normal cells, whereas others move equally fast on all stiffness levels (HCC-4006) or exhibit negative durotaxis on stiff matrix (PC9 cells). These findings warrant further investigation to identify the underlying molecular mechanisms. Finally, we have preliminary data showing that cells on soft substrate are more sensitive to the drug (Osimertinib) compared to stiff matrix.

Currently, we are setting up a system to study whether stiffness regulates the non-genetic mechanisms of drug resistance.

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[1] Barber-Perez N*, Georgiadou M*, Guzman C, Isomursu A, Hamidi H, Ivaska J. 2020. *J Cell Sci*, **133**(12): jcs242909.