Evaluation of cancer cells mechanical phenotype associated with the resistance to treatment in myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, characterized by an abnormal proliferation of leukemic cells (or blasts) that build up in the bone marrow and the blood. Despite the recent progress in therapies, which consist essentially in intensive cycles of chemotherapy or the use of targeted therapies, most of the AML patients do not recover, having a five-year survival rate of 20% (1). This poor prognosis may be explained by tumor cell heterogeneity, which could be related to cellular differentiation, as well as to the tumor microenvironment. Indeed, the rapid clonal expansion of leukemic blasts within the bone marrow alters the physical characteristics of the tumor microenvironment and decreases the available space for each cell type. This project seeks to establish a correlation between drug resistance and leukemic cell intrinsic stiffness, in the context of the dynamic dialogue between leukemic cells and their microenvironment.
One of the most widely utilized passive microfluidic methods in literature for measuring cellular mechanical properties with high throughput involves the monitoring of cell deformations as they flow passively through constricted channels (2). Here we propose an original readout traducing the way the cell perturbs the pressure distribution within the device, as it blocks the flow when passing through the constriction (3). Preliminary results suggest different mechanical profile associated with AML cell lines that are sensitive or resistant to chemotherapy, consistent with findings in the literature (4), hence demonstrating the pertinence of our approach. Furthermore, our data suggests that the mechanical properties of resistant AML cell lines may be treatment-dependent, varying with the applied therapeutic agent.

Moreover, our findings demonstrate that our microfluidic device allow for detecting alteration

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of the mechanical properties of drug-sensitive cells following short exposure to therapeutic drugs (as early as 2 hours). Indeed, we report an overall increase in the intrinsic rigidity of cells after treatment; this increased rigidity is the first stage of the cell death to come, hence traducing drug sensitivity, which is also reported in other studies (5).We confirm the relevance of our approach by evaluating the drug sensitivity of primary cells, specifically bone marrow and peripheral blood samples, examining their cell mechanics following a 2-hour chemotherapy exposure.

The long-term objectives of this study are to (i) to develop a device for personalized drug screening capable of rapidly (within 2 hours) identifying the most effective treatment for a patient's cells; and (ii) to detect the presence or emergence of cells with a resistant profile.

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