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Mechanical-control of cell proliferation increases resistance to chemotherapeutic agents

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While many cellular mechanisms leading to chemotherapeutic resistance have been identified, there is an increasing realization that tumor-stroma interactions also play an important role. In particular, mechanical alterations are inherent to solid cancer progression and profoundly impact cell physiology. Here, we explore the influence of compressive stress on the efficacy of chemotherapeutics in pancreatic cancer spheroids. We find that increased compressive stress leads to decreased drug efficacy. Theoretical modeling and experiments suggest that mechanical stress decreases cell proliferation which in turn reduces the efficacy of chemotherapeutics that target proliferating cells. Our work highlights a mechanical-form of drug resistance, and suggests new strategies for therapy.

Mechanical alterations of solid tumors are a hallmark of cancer progression. Among the many occurring modifications, the most representative forms of mechanical alterations in tumors are changes in extracellular matrix rigidity[1] and build-up of compressive stress[2]. Compressive stress accumulation can be found in many cancers such as glioblastoma multiforme[3] or pancreatic ductal adenocarcinoma (PDAC)[2].

PDAC is one of the deadliest cancers with extremely poor prognosis and no efficient treatment available besides surgery. PDAC development is characterized by excessive deposition of extracellular material and strong modifications of the mechanical environment. In particular, the accumulation of negatively-charged hyaluronic acid leads to electroswelling of extracellular matrix and subsequent compressive stress experienced by tumor cells[4]. The local growth of cancer cells in an elastic environment also leads to build-up of compressive stress through a process known as growth-induced pressure[5, 6]. PDAC tumors are extremely compressed, within the kPa range[7].

In vitro, compressive stress can alter cell physiology in multiple ways, from proliferation[8, 9] to migration[10, 11]. *In vivo*, it has recently been shown that compressive stress in PDAC tumors can exceed blood pressure and participate in vessel collapse[12]. Most of large vessels (diameter above 10μm) are clamped, leading to poor perfusion. Vessel collapse is associated with drug resistance: classical first-line chemotherapeutics such as gemcitabine are thought to be unable to reach the tumor, decreasing or even preventing the effect of the drug. Intravenous injection of a pegylated-form of hyaluronidase, an enzyme digesting hyaluronic acid, renormalizes blood vessels and, in combination with gemcitabine, increases chemotherapeutic efficacy[12].

The proposed mechanism overcoming this form of resistance is better tumor perfusion through decrease compressive stress. However, it remains unclear how the combination of hyaluronidase and gemcitabine really works. Indeed, if the vessels are so collapsed that gemcitabine does not penetrate the tumor, hyaluronidase should not have a better chance to reach it. Another potential explanation which does not depend on perfusion is that compressive stress could directly act on tumor cells and decrease the efficacy of gemcitabine. Experimentally, scarce instances of drug resistance stemming from mechanical stress have been observed for cells growing on substrata of different rigidities[13] or under shear stress[14], with no clear mechanism. In this letter, we wished to explore the paradigm of compression-modulation of drug resistance. We investigated the impact of mechanical stress on chemotherapeutic resistance, considering the case of a well-perfused genetically homogeneous tumor, *e.g.* no drug perfusion issues and no mutation-based resistance.

Given the complexity of a tumor, uncoupling the effect of biochemical and mechanical interactions is a daunting challenge. A good *in vitro* system is the multicellular spheroid as a mesoscopic tumor model: three-dimensional cellular aggregates which remarkably mimic the relevant physiological gradients of mitogens, oxy-

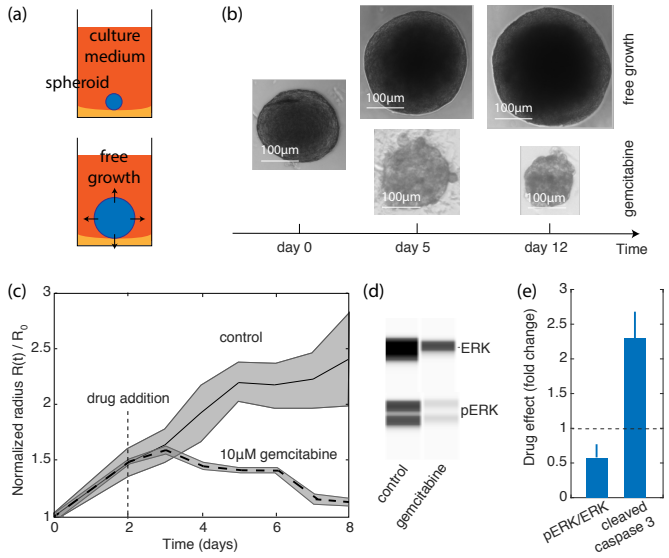


FIG. 1. Effect of gemcitabine on free growth. a. Schematic of free growing spheroid. b. Representative pictures of growing spheroids and one treated with gemcitabine after two days. c. Growth quantification over time. Median values normalized to time 0 ± SD over N ≥ 30 spheroids. d. Example of capillary western blot after 5 days under drug. e. Analysis of capillary wester blots. The data under gemcitabine treatment are normalized to the control. Mean ± SEM over N≥ 3 replicates. Data were pooled together. The quantity was renormalized by total volume of spheroids.

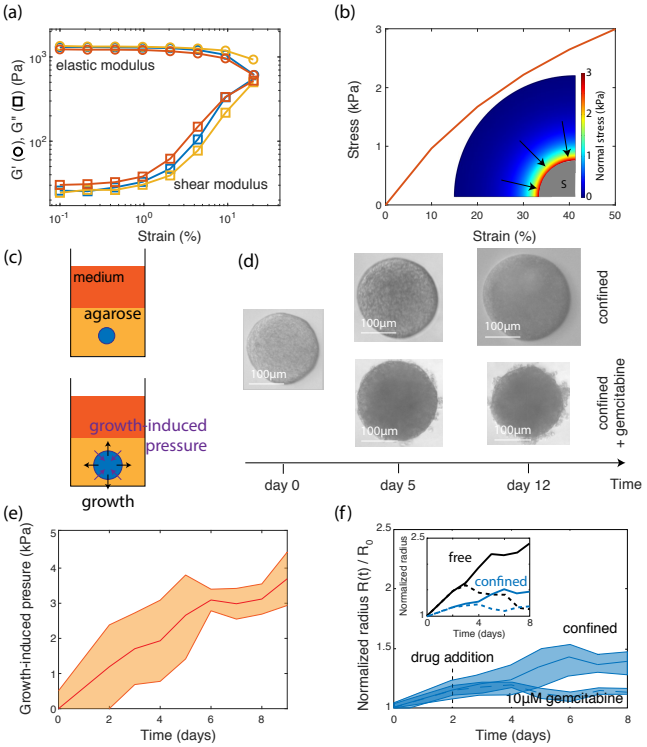


FIG. 2. Effect of gemcitabine on confined growth. a. Measurements of elastic (G', ○) and shear (G", □) moduli of 1% low-melt agarose. Different colors correspond to different forces used to hold the sample. b. Comsol simulation of a spheroid growing in a Neo-Hookean material modeled with parameters extracted from (a). Inset: Heat map of normal stress onto a spheroid (grey, S). c. Schematic of agarose-confined spheroid. d. Representative pictures of a confined spheroid and one treated with gemcitabine. e. Growth-induced pressure of spheroids in 1% low-melt agarose as a function of time. Median values normalized to time 0 ± SD over N ≥ 20 spheroids. f. Growth quantification of confined spheroids and treated ones with drug. Inset: Median curves for free (black) and confined (blue) spheroids, dashed lines correspond to gemcitabine treatment. Median ± SD over N ≥ 20 spheroids. Time 0 correspond to agarose confinement.

gen, or glucose. They have been extensively used as tumor model for the study of drug delivery[15]. Although their mechanical properties might differ from those of tumors, for many purposes, spheroids can be viewed as a tumor subunit. Because they do not have any biochemical crosstalk with their environment, spheroids are ideal to evaluate the impact of mechanical stress on tumor growth. We formed spheroids from a pancreatic $Kras^{G12D}$ cell line, representative of pancreatic cancer mutations[16], using a classical agarose cushion protocol[8] (Fig. 1a). Under normal growth conditions, spheroids grew over time in the hundreds of micrometer range (Fig. 1b). We restricted ourselves to the use of small spheroids (diameter below 400μm) to avoid chemical gradients. We detail in the Supplementary Information and Fig. S1 the statistics associated to the data.

We treated freely growing spheroids with gemcitabine to investigate the effect of this chemotherapeutic without mechanical stress. Gemcitabine is a cytidine-analog which activates within the cell into a deoxycytidine-triphosphate (dCTP)[17]. dCTP lead to cell death by creating an irreversible error upon DNA incorporation. Not surprisingly, we found that spheroids subjected to 10μM gemcitabine decreased in size (Fig. 1b). The decrease was apparent after an average of 1 day post-drug addition (Fig. 1c), consistent with the fact that only S-phase cells are sensitive to the drug. We performed capillary western blots to investigate the changes in proliferating and dying cells under gemcitabine treatment (Fig. 1d, see also Methods for protocol). We measured the ratio between a phosphorylated-form of ERK (pERK) over total ERK and the amount of cleaved-caspase 3 as a proxy for cells undergoing programmed cell death[18] (Fig. 1e). Even though gemcitabine can activate ERK[19], the latter is also a proxy for cell proliferation on long timescales[20]. We observed that the amount of pERK/ERK was halved after 5 days of treatment, and the amount of dying cells increased by roughly a factor 2, consistent with gemcitabine preferentially killing proliferating cells.

We next sought to investigate the impact of growth-induced pressure on the efficacy of gemcitabine. Several strategies have been developed to study cells under growth-induced pressure, such as microfluidic confining

chambers[21], embedding single cells in agarose or PEG-heparin hydrogels[5, 9] or in alginate shells[6], or directly embedding spheroids into alginate hydrogels[22]. In order to easily follow single spheroids, we opted for a strategy where spheroids were directly embedded into low-melting 1% agarose. Briefly, 200μL of a 2% low-melting agarose solution kept at 37°C was mixed with a 200μL solution containing a spheroid, and polymerized on ice to limit the rapid sedimentation of the spheroid. Gelling on ice was fast and did not affect the initial growth of the spheroids.

Measurement of growth-induced pressure requires careful characterization of material property, a point that is often disregarded, as reminded in [9]. Rheological measurements of agarose showed a plateau for low strain followed by an apparent softening of the material (Fig. 2a). Softening has also been observed and characterized in a recent study by Kalli et al.[23]. One cannot exclude the fact that slippage at the plate/sample interface in the rheometer could lead to this apparent softening - we used rough sandpaper during rheological measurement to avoid this effect. We wish to point out that in the case of lower agarose concentration (0.5%), one could reach a critical deformation of about 70% above which macroscopic rupture is observed, leading to an effective unconfinement of the spheroid (Fig. S2). This rupture could explain the softening observed at high strains. In our study, we used 1% agarose samples, kept the deformation below 70% strain and discarded the rare instances of "rugby-shaped" spheroids[24].

Incorporating softening into the Neo-Hookean material properties of a finite-element simulation of a spheroid growing in agarose[23] gave a rough linear increase of normal stress applied onto the spheroid during growth (Fig. 2b). This calibration can be used to extract growth-induced pressure curves from the growth of embedded spheroids (Fig. 2c). While other models like viscoelastic ones have been used to derive growth-induced pressure[25], we do not believe the qualitative variation and order of magnitude of the obtained data would strongly depend on the model chosen for small deformations. Expansion of agarose-embedded spheroids resulted in slower growth (Fig. 2d), similar to what has been described for other embedding solutions[5]. We found that growth-induced pressure rose to the kPa range over a period of a few days (Fig. 2e).

We added 10μM of gemcitabine after 2 days of confined growth and recorded size evolution. Interestingly, we observed that compressed spheroids were less sensitive to the chemotherapeutic than freely growing ones (Fig. 2f and Fig. S3): While unconfined spheroids decreased in size by roughly 30-40%, compressed spheroids decreased by less than 10% (inset of Fig. 2f).

Gemcitabine is a small molecule, slightly smaller than Hoescht 33342 DNA intercalent. We did not find any difference in Hoescht penetration in between a control and a compressed spheroid (Fig. S4), strongly suggesting that the observed effect of gemcitabine was not due

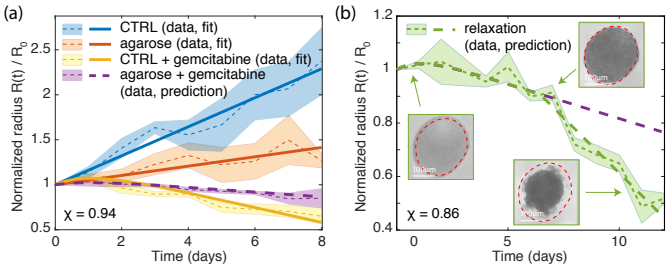


FIG. 3. Prediction of the model on confined data. a. Model plotted on confined spheroids exposed to gemcitabine (large dashed purple). Prediction score $\chi = 0.94$. b. At drug addition, $R(t = 0) \geq R(t = -2)$, while at about day 7, the radius decreases due to drug treatment to a value $R(t = 7) \sim R(t = -2)$ and become unconfined: subsequent decrease happens without mechanical stress. The model (large dashed green) captures this effect, switching from rate of confined cells (large dashed purple), to rate of unconfined cells. $\chi = 0.86$. In both cases, median values normalized to the time of drug addition $\pm$ SD over N $\geq$ 20 spheroids. Time 0 correspond to drug treatment.

to altered penetration of the drug under compression. Two non-mutually exclusive hypotheses can explain the effect of mechanics. The first one entails that compressive stress triggers mechanosensitive pathways directly acting on the effect of the chemotherapeutic, for instance on gemcitabine activation within the cell or import/export rates[17]. The second hypothesis is that compressive stress would trigger mechanosensors specifically decreasing cell proliferation[9, 22, 26], indirectly impacting chemotherapeutic efficacy. While capillary western blots could not be performed on agarose-embedded spheroids without biological perturbation, we performed immunostaining of the proliferation indicator Ki67[8] of paraffin-embedded samples and observed that compressive stress decreased cell proliferation (Fig. S5).

To the best of our knowledge, there is no study mentioning mechanosensitive pathways acting on the activity of the drug. Although we cannot rule out their existence, we developed a generic mathematical framework in order to get insight into the potential mechanism limiting drug efficacy under mechanical compression (see Method). We assumed that the total number of cells in the spheroid varied according to pressure-dependent cell proliferation and drug-induced death. Cell death without drug was considered negligible (see Note on cell death). Cell proliferation was exponentially distributed over the spheroid radius, with a pressure-independent characteristic length ℓ (Figs. S5 and S6). We observed that cell death induced by the drug is not instantaneous. Indeed, cells must be in a proliferative state for the drug to be effective. The waiting time for a cell to enter the proliferative phase could be assumed to be exponentially distributed, giving a delay for the drug to be effective of about 24 hours. We wrote the first-order temporal variation of the spheroid radius R as:

$$\dot{R} = (1-d)\frac{\gamma\ell}{\beta} = (1-d)g$$

where γ was the pressure-dependent cell proliferation rate and β a quantity accounting for spheroid compressibility (see Methods). Then, we denoted by g the effective growth velocity which accounted for potential changes in cell density, and by d the death term induced by the drug which included time delay (see Methods for full derivation). By construction, d linearly coupled the drug-induced death rate to the proliferation rate: if no cells proliferated, the death rate was zero. The dependence on pressure was only considered for the growth velocity g which took value g_0 in control conditions (i.e. no compression and no drug). We used a single growth curve to fit each parameter individually. In particular, $g = g_0$ was fitted through the control experiment, $g = g_c$ through the compressed spheroid, and the drug-induced death term $d = d_0$ through unconfined and drug-treated spheroids. Under the assumption that death and proliferation rates are similarly affected by mechanical stress (d is not a function of pressure), we predicted that the combined effect of mechanical stress and drug should lead to a growth velocity proportional to $(1-d_0)\,g_c$ on long timescales. The precision of the prediction was scored by a square difference of the measurement with the expected value. Our model remarkably predicted the experimental data (Fig. 3a), with a score $\chi = 0.94$, suggesting that, indeed, d did not depend on pressure. This independence indicated that mechanical stress mainly signaled to pathways implicated in cell proliferation rather than in the action of the drug.

Our model predicted that a decrease in compressive stress could lead to an increase in cell proliferation and a higher efficacy of the chemotherapeutic. Although we could not instantaneously relax mechanical stress without any biological perturbation, we took advantage of the fact that treated spheroids decreased in size over time. After 6-7 days of drug treatment, some spheroids saw their radius $R(t \geq 7)$ reducing below the initial inclusion size $R(t = -2)$ such that they were not anymore confined and did not experience compressive stress (pictures inset of Fig. 3b). Note that the spheroids presented in Fig. 3a were always confined. Within our framework, quiescent cells would re-enter the cell cycle, proliferate faster, and consequently die faster. Our model perfectly captured the experimental data (Fig. 3b, $\chi = 0.86$): a slow initial death velocity during compression, followed by a faster one in the unconfined phase.

The excellent agreement of the model with the experimental data was consistent with a mechanism where mechanics would decrease chemotherapeutic efficacy through a modulation of cell proliferation. This mechanism made two key predictions: If the efficacy of a proliferation-based chemotherapeutic decreased because of a modulation of cell proliferation, then the observed modulation of efficacy (i) should not depend on the type of drug used, but rather on the fact that the chemotherapeutic targeted proliferating cells, and, similarly, (ii) should not depend on the type of mechanical stress applied, but rather on the fact that mechanical stress could decrease cell proliferation. We investigated these two predictions, by treating with a different chemotherapeutic, docetaxel, and applying a different kind of mechanical stress, an osmotic compression with dextran [8].

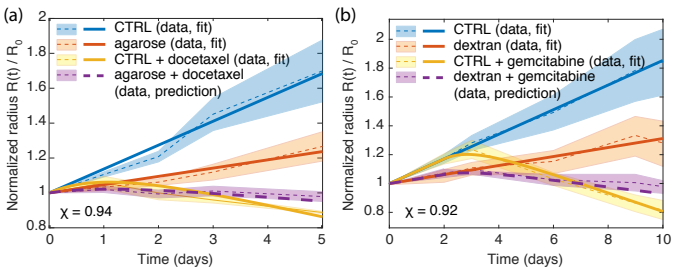


FIG. 4. Prediction of the model for (a) confined spheroids exposed to docetaxel ($\chi = 0.94$) and (b) osmotically compressed spheroids exposed to gemcitabine ($\chi = 0.92$). In both cases, median values normalized to the time of drug addition ± SD over N $\geq$ 10 spheroids for docetaxel and $\geq$ 30 spheroids for dextran. Drug was added at time 0 for (a) and at time 2 for (b).

Docetaxel is a taxol-based drug which stabilizes microtubules, leading to cell death during M-phase [27]. We confined spheroids in 1% low-melting agarose gel as previously described, and treated the spheroid after 2 days of compression with 10μM docetaxel. Our model predicted the experimental data, the efficacy being reduced for compressed cells, in a predictive manner ($\chi = 0.94$) (Fig. 4a).

The addition of high-molecular weight dextran to the culture medium reduced cell proliferation in a similar way as growth -induced pressure [8, 26, 28]: We observed that osmotically compressed spheroids restricted cell proliferation to the outermost layers (Fig. S5) with the same proliferation profile as the control (Fig. S6). While ERK could potentially be activated by mechanical stress[22], capillary western blots showed a decrease in pERK/ERK over long timescales, consistent with immunofluoresence staining of Ki67 (Fig. S7). Moreover, similar to what was previously found[8], increasing compression decreased growth rate (Fig. S8). Treatment of osmotically compressed spheroids with gemcitabine showed a qualitatively comparable modulation of efficacy of the drug with growth-induced pressure (Fig. 4b). Once again, our model remarkably predicted the effect of the drug combined to osmotic treatment ($\chi = 0.92$).

Many past studies have identified key features which can eventually lead to drug resistance. Most studies have focused on the inactivation of the drug by the host, the alteration of the drug target or DNA mutations that could create *de novo* resistance. While all of these mechanisms are cell-centered, there is an increasing realization that stromal components could also participate in drug resis-

tance.

Our experimental data suggest a novel mechanical-form of drug resistance which could arise from tumor-stroma mechanical interaction. Triggering of signaling cascade reducing the activity of a chemotherapeutic under mechanical stress seems not to be needed for resisting the drug. Rather, its efficacy can directly be altered by a mechanical-control of cell proliferation which can occur through dedicated sensors. The noteworthy theoretical prediction of the experimental data, with the underlying assumption that growth and drug-induced death rates are similarly affected by mechanical stress, strongly supports this mechanism [29]. We observed that growth-induced pressure, a highly common type of mechanical stress present in most solid tumors, can modulate the efficacy of chemotherapeutics acting on different parts of the cell cycle. Moreover, an osmotic compression, stress of very different origin and sensing which could arise due to accumulation of oncotic pressure [30] also led to similar modulation of chemotherapeutic. There are now evidences that quiescence is one major mechanism leading to drug resistance [31] and that mechanics can turn cells towards quiescence [8, 32]. However, to our best knowledge, no quantitative models linking mechanics to drug resistance through a direct modulation of proliferation have been proposed so far.

In this study, we only considered the case of an inert and homogeneous stroma mechanically interacting with a tumor spheroid. The complexity of a real microenvironment with extracellular matrix signaling on cell proliferation could as well play a role in the efficacy of chemotherapeutics [33–35]. Similarly, larger levels of mechanical stress could lead to unforeseen mechano-chemical crosstalk. We notably observed that our prediction became worse for higher concentration of dextran (Fig. S9). While we cannot exclude unknown effects of dextran itself, this observation suggested a non-linear coupling between death and growth rates and potential signaling to pathways implicated in drug activation.

Most if not all solid tumors experience compressive stress. This stress can be heterogeneous *in vivo* creating pockets of drug-resisting compressed cells. Within the framework of a mechanical-form of drug resistance, it clearly appears that the mechanical modulation of the microenvironment could be an interesting therapeutic option. For instance, hyaluronidase, which is currently under clinical trial, may have a very different effect than only modulating tumor perfusion: by reducing matrix swelling and subsequent compressive stress experienced by cells, it could also modulate cell proliferation. A direct mechanical-modulation of drug efficacy through cell proliferation could appear particularly deleterious, notably because it does not rely on any specific gene alteration targeting the mode of action of the drug.

In conclusion, a mechanical-form of drug resistance calls for a better understanding of the mechanosensors at play leading to proliferation reduction: A therapy targeting these sensors to enforce cell proliferation under mechanical stress coupled with a proliferation-driven chemotherapeutic could represent an appealing strategy to battle compressed tumors.

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