Abstract
The stress harbored by the solid phase of tumors is known as solid stress. Solid stress can be either applied externally by the surrounding normal tissue or induced by the tumor itself due to its growth. Fluid pressure is the isotropic stress exerted by the fluid phase. We recently showed that growth-induced solid stress is on the order of 1.3 to 13.0 kPa (10–100 mmHg) – high enough to cause compression of fragile blood vessels, resulting in poor perfusion and hypoxia. However, the evolution of growth-induced stress with tumor progression and its effect on cancer cell proliferation in vivo is not understood. To this end, we developed a mathematical model for tumor growth that takes into account all three types of stresses: growth-induced stress, externally applied stress, and fluid pressure. First, we conducted in vivo experiments and found that growth-induced stress is related to tumor volume through a biexponential relationship. Then, we incorporated this information into our mathematical model and showed that due to the evolution of growth-induced stress, total solid stress levels are higher in the tumor interior and lower in the periphery. Elevated compressive solid stress in the interior of the tumor is sufficient to cause the collapse of blood vessels and results in a lower growth rate of cancer cells compared with the periphery, independently from that caused by the lack of nutrients due to vessel collapse. Furthermore, solid stress in the periphery of the tumor causes blood vessels in the surrounding normal tissue to deform to elliptical shapes. We present histologic sections of human cancers that show such vessel deformations. Finally, we found that fluid pressure increases with tumor growth due to increased vascular permeability and lymphatic impairment, and is governed by the microvascular pressure. Crucially, fluid pressure does not cause vessel compression of tumor vessels. Cancer Res; 73(13); 3833–41. ©2013 AACR.

Introduction
The mechanical microenvironment of solid tumors is characterized by both fluid- and solid-phase stresses. Fluid-phase stresses include the vascular and interstitial fluid pressures (IFP), as well as the shear stresses exerted by the blood flow on the vessel wall. Solid-phase stresses include the compressive and tensile stresses exerted by the non-fluid components. Solid stresses are divided into 2 categories: the externally applied stress, which is developed through mechanical interactions between the solid components of the growing tumor and the...
surrounding normal tissue, and the growth-induced stress, which is stored within the tumor as the proliferating cancer and stromal cells strain structural components (e.g., collagen, hyaluronan) of the tumor microenvironment. This growth-induced stress is retained as a "residual stress" that remains in the tumor even after the tumor is excised and external confining stresses from surrounding tissues have been removed (1, 2). Previously, we investigated the external and residual stresses separately. Using in vitro models of tumor spheroids grown within a polymer matrix, we found that increasing the stiffness of the matrix the stress exerted from the matrix on the spheroids inhibits tumor growth by inducing cancer cell apoptosis and reducing proliferation, determines the shape of a tumor, and alters gene expression (3–5). In addition, externally applied compressive stresses induce invasive phenotype in cancer cells grown in a monolayer (6). As far as residual stresses are concerned, we recently estimated residual stress levels in murine and human tumors to be on the order of 1.3 to 13.3 kPa (10–100 mmHg), which is sufficient to compress and eventually collapse the fragile blood and lymphatic vessels associated with tumors (2). Furthermore, we identified cancer cells, stromal cells, and the extracellular matrix as key tumor components that contribute to the generation and accumulation of these stresses. However, how growth-induced solid stresses evolve in situ in a tumor and its surrounding tissue during tumor progression and how this affects the tumor microenvironment or cancer biology is not known.

To this end, here we present a mathematical model of tumor growth that takes into account the combined effect of external and growth-induced solid stresses as well as the IFP in the tumor mechanical microenvironment. We first conducted ex vivo experiments to determine the evolution patterns of growth-induced stress. Subsequently, we incorporate this information into our mathematical model and carry out simulations to investigate how growth-induced solid stress affects the mechanical microenvironment of tumors and the proliferation of cancer cells. Our model predicts, and we confirmed it with clinical biopsies from patients with cancer, that solid stress in the tumor periphery deforms blood vessels into elliptical shapes, which might have an adverse effect on their function. Finally, we apply a biphasic formulation into the model to incorporate the fluid pressure and find that IFP increases during tumor growth due to increased vascular permeability and lymphatic impairment, but it does not cause vessel compression.

Materials and Methods

Animal and tumor models

Tumors were prepared by implanting a small piece (1 mm³) of viable tumor tissue from pre-prepared in vivo source tumors into severe combined immunodeficient (SCID) or Friend virus B-type (FVB) mice. The implantation sites included the mammary fat pad (MFP), the pancreas, and the flank. Specifically, we used the following cell lines: murine mammary adenocarcinoma E0771 (SCID, orthotopic-MFP), murine pancreatic adenocarcinoma AK4.4 (FVB, orthotopic-pancreas), human...
melanoma Mu89 (SCID, orthotopic-flank), and human glioblastoma U87 (SCID, ectopic-flank). The E0771 breast cancer cell line was originally established by Dr. F.M. Strotak at the Memorial Sloan–Kettering Cancer Center (New York, NY) and kindly provided by E. Mihich (Roswell Park Memorial Institute, Buffalo, NY) in 2008. AK4.4 cells (KrasG12D and p53−/−) were kindly provided by Dr. Nabeel Bardeesy (Massachusetts General Hospital, Boston, MA) and were isolated from spontaneous pancreatic tumors in genetically engineered mice (Ptf1-Cre/+/LSL-KrasG12D/p53−/−) in 2011 (9). Mu89 cells were obtained by Dr. J.T. Kurnick (Massachusetts General Hospital) and U87 cells were obtained from the American Type Culture Collection, both in 1998. The cell lines were not tested at the time of experiment. For each tumor type, 7 to 15 specimens were used.

Measurement of the evolution of growth-induced solid stress

Growth-induced stress was quantified by applying a mathematical model to a measurement of the relaxation of an excised tumor after making a cut along its longest axis (2). When the tumors reached a size ranging from 4 to 10 mm, the animal was anesthetized by injecting 0.2 mL ketamine–xylazine (100/10 mg/kg body weight, intramuscularly), the tumor was excised and washed with Hank’s Balanced Salt Solution (HBSS), and its 3 dimensions were measured by a caliper. Then, the tumor was cut along its longest axis through approximately 80% of its thickness and allowed to relax for 10 minutes to let any poroelastic response diminish. Afterward, the resulting relaxation (i.e., tumor opening in Fig. 1) was measured at the surface of the tumor between the 2 hemispheres. In an excised tumor, the externally applied stress vanishes and only growth-induced stress is retained in the tissue. The retraction of the tumor at the periphery after the cut is indicative of growth-induced tensile stress, while the swelling of the inner surface is indicative of growth-induced compressive stress in the interior of the tumor. By putting the measurements of tumor relaxation into our mathematical model (2), we calculated the residual stretch ratio, λ, in the tumor interior and the periphery. Subsequently, we constructed plots of the residual stretch ratio, λ, as a function of the relative increase in tumor volume (V/V0) and fit Eq. B to the data to derive the values of the parameters A1, B1, A2, and B2 (Fig. 2, Supplementary Fig. S1 and Table S1). V0 is a reference volume that corresponds to the volume of a spherical tumor with diameter 500 μm (V0 = 0.065 mm3). At this size, solid stresses start to become significant and, at the same time, the tumor is large enough to be considered as a continuum (10).

Cancer-cell proliferation measurement

Murine pancreatic adenocarcinoma tumor chunks (~1 mm3) were implanted in the pancreas of FVB male mice and resected when the diameter was approximately 8 mm. These tumors were fixed in paraformaldehyde and frozen in optical cutting temperature (OCT). Then, 10 μm thick frozen sections were stained with Ki-67 (DAKO) and imaged by confocal microscopy. Four peripheral and 4 interior images were taken. Peripheral areas were defined as within 1 field of view (~700 μm) from the tumor boundary. Ki-67 area fractions were determined using a custom MATLAB program through intensity and size thresholding.

Human samples

Five-micrometer thick hematoxylin and eosin-stained formalin-fixed paraffin-embedded sections of 100 unidentified samples of different carcinomas and sarcomas diagnosed at the Massachusetts General Hospital were evaluated by an anatomic pathologist (M. Snuderl). Peripheral areas of each tumor were evaluated for deformed arterioles and venules in proximity of the infiltrating or pushing tumor margin. Circumferential cross sections, perpendicular to the long axis of the vessel, were selected on the basis of histopathologic features of the vascular wall, while longitudinal and tangential cross sections of vascular lumen were excluded from analyses.

Formulation of the mathematical model

A detailed description of the mathematical model can be found in the Supplementary Materials. We assume a tumor to be a sphere with an initial diameter of 500 μm. The tumor is surrounded by normal tissue and, because of symmetry, we solved for one-eighth of the domain (Supplementary Fig. S2). The mechanical behavior of the tumor is modeled as isotropic and Neo-Hookean. The shear modulus, μ, was set to 20.0 kPa while separate simulations were run for the cases of nearly incompressible and compressible tumors with Poisson ratio ν = 0.45 and 0.2 (8, 11). The surrounding normal tissue was also modeled as isotropic and Neo-Hookean with modulus 10.0 kPa and Poisson ratio 0.2 (12). In Eq. (A), the values of the parameters λmax, a, and β were found by fitting the model to experimental data for the growth of orthotopic E0771 tumors (Supplementary Fig. S3). The values were λmax = 25.0, a = 0.3/day, and β = 2.5 × 10−5 /Pa. The model equations were solved using the commercial finite element software Comsol.
Results

Residual stretch ratio follows a bi-exponential function with respect to tumor volume

The evolution of growth-induced solid stress quantified by the “tumor opening” is shown as a function of the relative volume of the tumor (V/V_o) for 3 orthotopic (Mu89, E0771, and AK4.4) and 1 ectopic (U87) tumor model (Fig. 2 and Supplementary Fig. S1). The tumor opening is indicative of the magnitude of the growth-induced stress stored within the structural components of the tumor. As the volume of the tumor increases, the opening increases. This suggests that growth-induced stress is accumulated in the tumor during growth. On the basis of these experimental data and using our previously developed methodology (Supplementary Materials; ref. 2), we calculated the residual stretch ratio, \( l_r \), in the intratumoral region and the periphery. In the absence of growth-induced stress, \( l_r = 1 \). For tensile growth-induced stress, \( l_r \) takes values in the range of 0 and 1, whereas for compressive growth-induced stress, \( l_r \) is greater than 1. The residual stretch ratio fits a biexponential function (Eq. B) for all tumor types (Fig. 2 and Supplementary Fig. S1). The values of A1, B1, A2, and B2, estimated from the best fit, are presented in Supplementary Table S1.

Growth-induced solid stress modulates the mechanical microenvironment of solid tumors

We used our model to calculate the spatial distribution of the total solid stress in tumors. The total solid stress includes contributions from both the growth-induced stress and the externally applied stress developed due to mechanical interactions between the tumor and the surrounding normal tissue. Therefore, for these results we account only for the solid phase of the tumor; a biphasic formulation to include the interstitial fluid is presented later in our analysis. Figure 3A shows the spatial distribution of the radial stress component as a function of the distance from the tumor center for 4 time points and obtaining the values of the residual stretch ratio from the data of the E0771 tumor. Figure 3B presents the radial stress at the end of the simulation (day 18) either neglecting residual stresses or taking the residual stretch ratio from the E0771 (low residual stress) and Mu89 (high residual stress) data. In agreement with previous studies (8, 13), the radial stress is compressive and almost uniformly distributed in the center of the tumor and goes to zero as we move away from the tumor center. Beyond these 2 previous studies, our model predicts that generation of residual stresses can cause a 30% (\( \sim 6 \text{ kPa} \)) increase in the compressive stress at the interior of the tumor.
This increase in overall compressive stress is within the range of residual stress levels we measured previously, suggesting that externally applied and growth-induced stresses are additive.

Figure 3C depicts the spatial distribution of the circumferential stress component for 4 time points using the values of the residual stretch ratio from the data of the E0771 tumor. The model predicts an almost uniform distribution of compressive circumferential stress at the center of the tumor. Circumferential stress decreases close to the tumor periphery and turns rapidly to tensile at the normal tissue interface with the tumor. Subsequently, it decreases gradually to zero. Figure 3D presents the circumferential stress at the end of the simulation (day 18) for 2 cases of residual stress levels: (i) no residual stress, and (ii) residual stress taken from the Mu89 data. Residual stresses result in increased levels of circumferential compression at the interior of the tumor and a smoother transition of the stress from compressive to tensile at the interface with the normal tissue. Finally, comparison of Fig. 3B and D shows that, at the center of the tumor, the radial and circumferential components of the stress are similar, but they become different toward the periphery.

### Growth-induced solid stress contributes to spatial heterogeneity in cancer cell proliferation

Our model accounts for cancer cell growth (proliferation minus apoptosis) with the stretch ratio, $\lambda_g$. In Figure 4A, we plot $\lambda_g$ as a function of the distance from the center of the tumor and from day 6 to day 18. The results reveal 2 interesting insights. Firstly, in the beginning of tumor growth, $\lambda_g$ is uniform throughout the tumor. As the tumor progresses and growth-induced stress is accumulated, a spatial heterogeneity in $\lambda_g$ is observed. Cancer cell growth is higher at the periphery compared with the interior of the tumor. Secondly, growth-induced stress increases the relative growth of cancer cells, $\lambda_g$, between the periphery and the interior of the tumor as shown in Fig. 4B. This can be explained by the fact that, in the interior of the tumor, the compressive stresses are higher than the stresses at the periphery and, thus, in the center, cancer cell growth is inhibited to a larger extent. To further validate the results of our model, we measured proliferation in the AK4.4 tumors based on the fraction of Ki-67–positive tumor cells. We found cell proliferation in the periphery to be higher than in the interior of the tumor with a relative proliferation ratio of 1.1, within the range of the model predictions. It is important to point out that solid stress can inhibit cancer cell growth in 2 ways. The first way is by directly compressing cancer cells. The second, indirect way is by compressing blood vessels and creating hypoxia. Solid stress and hypoxia not only impede proliferation and induce apoptosis but also enhance the invasive and metastatic potential of cancer cells (Fig. 5A and B). In our analysis, we accounted only for the direct effects of solid stress.

### Solid stresses at the tumor periphery compress blood vessels to elliptical shapes

A schematic of the profile of solid stress in tumors and the resulting deformation of the tissue is shown in Fig. 5A. In the interior, the tumor is compressed, which could collapse blood vessels (14), while at the interface with the normal tissue the tumor is compressed in the radial direction and stretched in the circumferential. As a result of these stresses, peritumoral...
vessels might form elliptical rather than circular shapes. Indeed, Fig. 6 shows histologic sections of a murine and different human tumors, respectively. These images show how peritumoral vessels (both arterioles and venules) are deformed or collapsed. The aspect ratio (the ratio of the minor to the major axis) of the vessels measured was found to range from 0.01 to 0.5 (Supplementary Table S2).

**IFP cannot compress blood vessels**

To study the evolution of IFP in solid tumors, we used a biphasic formulation in our model to account for the interstitial fluid (details in Supplementary Materials). Notice that incorporation of the fluid phase will affect the total stress in the tumor (i.e., the sum of solid stress and fluid pressure) but not the solid stresses presented in Fig. 3. The solid phase was taken to be compressible with a Poisson ratio 0.45 and shear modulus 20 kPa. The hydraulic conductivity of the normal vessel wall, \( L_p \), was considered to be \( 3.6 \times 10^{-8} \text{ cm/mmHg-s} \) (15). In tumor vessels, the production of cytokines that increase vascular hydraulic conductivity and permeability (e.g., VEGF) increases with tumor growth and tumor growth is dependent on time. Therefore, we selected the tumor \( L_p \) to be a linear function of time starting from the value of the normal tissue and, at day 10, \( L_p \) becomes that of a tumor, that is, \( L_p = 2.8 \times 10^{-7} \text{ cm/mmHg-s} \) (15). Changing this time-dependence to a nonlinear function will only change the results qualitatively. The hydraulic conductivity of both the normal and tumor interstitial space, \( K \), was set to \( 1 \times 10^{-8} \text{ cm}^2/\text{mmHg-s} \), the vascular density \((S/V)\) to 70 and 200 cm \(^{-1}\), for the normal and tumor tissues, respectively, and the vascular pressure was taken to be 30 mmHg (15). The boundary conditions employed for the biphasic simulations are shown in Supplementary Fig. S4. A comparison of model predictions with experimental data for the evolution of IFP as a function of tumor volume is shown in Supplementary Fig. S5 while Fig. 7A presents the IFP changes with time. The pressure increases and, after 10 days, it becomes 11.7 mmHg, which is lower than the microvascular pressure (MVP).

Some investigators have considered pancreatic tumors as a closed system with collapsed, non-leaky vessels and no fluid exchange with the surrounding normal tissue (16). This hypothesis, however, contradicts recent clinical findings that gemcitabine combined with nab-paclitaxel (Abraxane) improves overall survival of patients with pancreatic adenocarcinomas (PDAC; ref. 17). In addition, gemcitabine plus PEGPH20 has been shown to improve PDAC response in
animal models (18). The size of both PEGPH20 and Abraxane (following disintegration in plasma) is approximately 10 nm (19). The fact that PDACs are responsive to these drugs implies that these drugs can extravasate from at least some vessels in these desmoplastic tumors to access stromal and cancer cells. Therefore, PDACs can only be an open system, just like any other tumor type, although with reduced vascular density due to extensive vessel compression (2, 18). A measure of the vascular density and leakiness that has been used in pertinent studies is the quantity \( \theta = \sqrt{L_p S \kappa / V} \) (15, 20). The lower the value of \( \theta \), the more hypovascular and less leaky a tumor becomes. Figure 7B shows the spatial distribution of IFP at day 10 and for 4 different values of \( \theta \). As the tumor vascular density and permeability decrease, the interstitial pressure goes to 0, whereas for abundant and hyperpermeable vessels, IFP becomes equal to the MVP. These results support the widely accepted concept that MVP is the principal driving force for interstitial hypertension (21) and, thus, IFP cannot compress blood vessels as changes in IFP will equilibrate with changes in the vascular pressure without affecting the vessel diameter. The effect of \( \theta \) on the total stress is shown in Supplementary Fig. S6. Another regulator of IFP is the hydraulic conductivity of the tumor interstitial space. The extracellular matrix of PDACs is very dense compared with normal matrix and contains charged fibers. Therefore, it is expected to have a lower hydraulic conductivity. In Supplementary Fig. S7, an analysis is conducted to show the effect of the tumor conductivity on IFP, keeping the vascular density \((S/V)\) to a low value of 15 cm\(^{-1}\). Again, the IFP is driven by the MVP even for a very low vascular density and tumor hydraulic conductivities.

Discussion

Although the existence of growth-induced solid stress in tumors was suspected for a long time, it was only recently that we developed a technique to estimate growth-induced stress levels from freshly excised murine and human tumor tissues (2). In our previous experimental studies (3–5), we accounted only for the effects of external stresses. Previous mathematical models incorporated growth-induced stress (22–24) but lacked quantification of these stresses. The scope of the current study was to investigate the combined
effect of external and growth-induced solid stresses on the biomechanical behavior of tumors and vessel morphology. We first conducted experiments and found that the dependence of growth-induced stress on tumor volume can be described by a bi-exponential relationship. Subsequently, we used this information in our mathematical model and showed that growth-induced and external stresses are additive in tumors and they both contribute to a tumor's mechanopathology. Specifically, our model predicted that growth-induced stress can cause a 30% increase in the overall tumor stress and, thus, contributes to the deformation of tumor blood vessels. It can also result in spatial heterogeneity of cancer cell growth with higher rates at the periphery of the tumor compared with the interior. The model suggests that the heterogeneity in cancer cell growth, which has been shown experimentally here and in other studies (3, 5), is more pronounced at higher growth-induced stress levels. Apart from this direct effect of solid stress, another indirect effect comes from the compression of blood vessels. In the interior of the tumor, many vessels are collapsed, which results in hypoxia and necrosis. In the periphery, vessels are deformed (Fig. 6), but they still are functional and have a higher vascular density and nutrient supply compared with the interior of the tumor (25, 26).

Solid stress versus IFP
IFP and solid stress, as stated in the Introduction, are entirely different entities. Although compressive solid stress can collapse fragile blood and lymphatic vessels in tumors, elevated IFP cannot (21). The elevated IFP is a result of fluid leaking from the blood vessels in tumors as well as the inability of the intratumor lymphatics to drain this fluid effectively (15, 27, 28). An understanding of causes and adverse consequences of the interstitial hypertension in tumor progression and treatment has led to clinically translatable strategies to lower tumor IFP in animal models and cancer patients (29, 30). Similar translatable strategies for alleviating solid stresses are likely to benefit cancer treatment further.

Sensitivity to model parameters
The solid-mechanical behavior of tumors depends on their stiffness and compressibility. The results presented in Fig. 3 correspond to a near incompressible tumor with stiffness 20 kPa. Simulations were also conducted for stiffer and compressible tumors. Supplementary Fig. S8 shows the effect of stiffness, and Supplementary Fig. S9 shows the effect of compressibility, on the mechanical response of a tumor. For incompressible tumors, an increase in the stiffness has a minor effect on the mechanical stresses. Mechanical stresses, however, decrease significantly as the tumor becomes more compressible.

The main purpose of the current study was to investigate the effects of growth-induced stress on the mechanical behavior of the tumor. The model consists of a large number of parameters used to define the proliferation and residual stretch ratios. The parameters of the residual stretch ratio, λ, (Eq. B) were independently calculated from experimental data on tumor opening (Fig. 2). The proliferation stretch ratio, λ, is a function of the parameters α, λmax, and β (Eq. A). The values of these parameters were also determined independently by fitting the model to the experimental data for the growth of E0771 adenocarcinomas (Supplementary Fig. S3). Supplementary Fig. S10 presents a parametric analysis varying the values of α, λmax, and β. Model predictions are sensitive to changes in each of these values. Sensitivity analysis was also carried out for the effect of vessel leakiness and density as well as the tumor hydraulic conductivity on IFP (Fig. 7B and Supplementary Fig. S7).

Limitations of the mathematical model
Our mathematical approach is subject to certain assumptions and limitations. We made the assumption of isotropic proliferation of cancer cells and generation of growth-induced stress. In addition, we used the Neo-Hookean constitutive equation to describe the mechanical behavior of the tumor and normal tissue. Tumors, as most biologic tissues, are complex and heterogeneous structures and an isotropic, continuum-level constitutive equation, like the Neo-Hookean model, might not be sufficient to fully describe their mechanical response. In addition, the behavior of the tumor may be more nonlinear than a Neo-Hookean material, which could increase peak stresses and affect growth distributions considerably. Furthermore, in the biphasic formulation we assumed that MVP remains constant in time and space. MVP, however, is not the same throughout the tumor and, in addition, as tumors progress and compress the "draining veins," MVP increases, thus causing an increase in IFP until they reach a plateau (21). Another limitation of our approach is that multiple combinations of λ at the interior and the periphery of a tumor might give rise to the same tumor opening. For the calculation of λ, we made the assumption that the residual stretch ratios at the periphery versus the interior of a tumor are symmetric with respect to unity. Other pairs of λ might also exist. The experiments have shown that the residual stretch ratio in the periphery will be always tensile (λ < 1), whereas the ratio in the interior of the tumor will be compressive (λ > 1). Therefore, the basic conclusions of our study should not be affected by the choice of λ provided it is taken to be tensile in the periphery and compressive in the interior. As more data become available, the model parameters can be refined, but, qualitatively, they will remain the same. Finally, we assumed cancer cell proliferation to follow Gompertz law. Gompertz law has been widely used to describe the growth of tumors, although it is a phenomenologic expression (7). Our mathematical framework is general and can incorporate more sophisticated models for the proliferation stretch ratio, λ, taking into account other parameters such as the concentration of oxygen and/or nutrients (8, 31, 32).

Disclosure of Potential Conflicts of Interest
R.K. Jain is employed (other than primary affiliation; e.g., consulting) as a co-founder and board member in XTuit Pharmaceuticals and H&Q Healthcare Investors and H&Q Lifesciences Investors; has a commercial research grant from MedImmune, Roche, and Dyax; has ownership interest (including patents) in XTuit Pharmaceuticals; and is a consultant/advisory board member of Enlight Biosciences, SyndeRx, Dyax, Noxxon Pharmaceuticals, and Zyngenia. No potential conflicts of interest were disclosed by the other authors.
Evolution of Solid and Fluid Stresses in Tumors

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References
Coevolution of Solid Stress and Interstitial Fluid Pressure in Tumors During Progression: Implications for Vascular Collapse

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