GROWTH-INDUCED STRESS IN TUMORS: IMPLICATIONS FOR CANCER PROGRESSION AND TREATMENT

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Introduction

Growth-induced stresses are generated in solid tumors due to the uncontrolled growth of cancer cells within the confined space of the normal tissue [Stylianopoulos, 2012]. These stresses can contribute to tumor progression and pathological cellular behaviour. Furthermore, they might compress blood vessels [Padera, 2004], reducing tumor perfusion and the systemic administration of drugs. In this work, we developed a strategy to quantify growth-induced stresses in murine tumors and studied the effect of stress on tumor growth and perfusion.

Methods

Growth-induced, residual, stress can be retained as stress after a tumor is excised, even though external confining forces have been removed. The existence of this stress is realized when one makes a cut to the excised tissue along its main axis, the stress relaxes and the tissue deforms in a measurable way. To calculate the stress from the measured deformation, we developed a computational model assuming that tumors mechanical behaviour is compressible and neo-Hookean and applying an existing theory for tissue growth [Rodriguez, 1994].

We employed five tumor models (n=12, Table 1) grown in severe combined immunodeficient (SCID) mice and measured the tumor growth rate given by the doubling time. Then we used our methodology [Stylianopoulos, 2012] to quantify growth-induced stress. Subsequently, tumor sections were obtained and stained with CD31 antibody for endothelial cells to indentify vascular structures and with lectin to measure tumor perfusion. Finally, therapeutic depletion of tumor stroma was performed with administration of Saridegib, 40 mg/kg for 8 d.

Results

Growth-induced stress was confirmed in all tumor types considered in this study. The stress was compressive at the center of the tumor and switched to tensile at the tumor periphery. Table 1 presents the results of the doubling time and the estimated by our model radial stress at the center of the tumor.

Cancer cell line	Doubling time (days)	Radial stress (mmHg)
U87	5.18	38.0 - 60.1
B16F10	0.94	2.8 - 4.7
E0771	2.21	4.9 - 8.2
MCaIV	2.50	4.5 - 7.4
4T1	2.25	5.3 - 8.8

Table 1. Doubling time and compressive radial stress. U87 is a glioblastoma, B16F10 a melanoma and E0771, MCaIV, and 4T1 mammary adenocarcinomas.

From CD31 and lectin staining we found the mean vessel diameter of tumors to be 10 μm and only the 32% of the vessels was perfused. Depletion of tumor stroma with Saridegib alleviated stress levels and resulted in a 10% increase in vessel diameter and a 47% increase in the fraction of perfused vessels.

Discussion

Our results suggest that depending on tumor type, growth-induced stress in tumors varies from 2.8 to 60.1 mmHg. Interestingly, we found that tumors with the highest stress level (U87) had the slowest growth rate (i.e., the highest doubling time). In addition, we found that stress alleviation can be achieved by depleting tumor stroma and it can cause the decompression of blood vessels and an increase in perfusion, which is essential for effective delivery of drugs. Our research demonstrates the potential of a new therapeutic strategy - the anti-stress therapy - to improve perfusion and drug delivery in solid tumors.

References

Padera *et al.*, Nature, 427: 695, 2004.

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Stylianopoulos *et al.*, PNAS, 109: 15101-15108, 2012.