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Review

The role of pressure in cancer growth*

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Abstract. The response to external mechanical forces is increasingly seen as a crucial aspect of cancer growth and a topic where the contribution of physics ideas and methods is important. Understanding if tumor progression towards increased malignancy reflects the geometry and mechanics of the microenvironment is an important issue still to be fully explored. In order to grow, tumors have to overcome the mechanical resistance posed by the tissues in which they originate, while cancer cells involved in metastasis are often subject to fluid pressure. Here we review the recent literature describing the role of solid and fluid pressure on tumor growth and progression. We discuss a variety of *in vitro* experiments as well as computational models used to interpret them. We conclude discussing future perspectives.

1 Introduction

The key issue to address in cancer research is the formation of metastasis. In recent years, increasing experimental evidence points out that tumors are not only affected by biological factors, but mechanical forces also play a role in tumor initiation, growth and metastatic transformation. To define the general role of mechanical forces on the behavior of a cell, we have first to understand how the cell senses and integrates exogenous mechanical signals within its tissue microenvironment, and thereafter how the cell coordinates its response as part of a multicellular, organized tissue structure. Changes in this delicate balance seem to be strictly correlated to the biological characteristics of a tumor and in particular could play a key role in the metastatic process.

The mechanical microenvironment of solid tumors is characterized by solid- and fluid-phase stresses. Fluid-phase stresses include the vascular and interstitial fluid pressures (IFP). Solid-phase stresses include the compressive and tensile stresses exerted by the non-fluid components, *i.e.* extracellular matrix (ECM), stromal and neighboring cells. Fluid stresses are mainly isotropic and hydro-statics and -dynamics in nature, while solid stresses are in general isometric and strongly dependent on the compliance of the surrounding environment. According to recent evidences, both fluid and solid stresses can contribute to promote tumor invasiveness and malignancy [90], although the precise mechanism by which they interplay into the cytoskeleton mechanics and they influence the tumor phenotype remains largely unclear. Besides that, fluid- and solid-phase stresses are both responsible of force-dependent activation of (often overlapping) signaling cascades, allowing the cells to respond quickly to a dynamic force environment, a process called mechanotransduction. From a systems biology perspective therefore, it may be risky and meaningless to pursue a separate analytic treatment of the effects of solid- and fluid-phase stresses on tumors, since everything is connected with everything in a cell [35].

The present review aims at revising the recent literature, furnishing new perspectives and ideas for both biologists and physicists involved in tumor research, focusing in particular on the role of solid and fluid stress in tumor evolution.

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2 Solid stresses in tumor growth

Tumors grow to the expense of normal tissues, indeed space limitations give rise to non-fluid–related pressure, *i.e.* solid stress. This stress depends on tumor size and local mechanical properties, which are influenced by tumor-associated ECM modifications (degradation, crosslinking, overproduction), an altered tissue tensional homeostasis [5, 84,91], increased compression force due to the solid state pressure exerted by the expanding tumour mass [73], matrix stiffening due to the desmoplastic response [74]. Solid-phase stresses are prominent in lowly deformable sites such as cranium and bone causing detrimental morbidity.

Stresses can be divided into two categories: the externally applied stress, which is developed through mechanical interactions between the solid components of the growing tumor and the surrounding tissue, and the growth-induced stress, which is stored within the tumor as the proliferating cancer and stromal cells modify the structural components of the tumor microenvironment. This growth-induced stress is referred to as a "residual stress", because it remains in the tumor even after the tumor is excised and external confining stresses from surrounding tissues have been removed [88,90,89].

The role of mechanical stress on tumor progression is rather controversial. Indeed, *in vitro* recent experiments have provided the evidence that tumor growth is considerably hindered by the presence of a surrounding constraining medium, as for instance a stiff matrix. Past studies, on the other hand, have also suggested that changes of ECM structure or mechanics, such as whether the matrix is stiff enough to resist cell traction forces, might actively contribute to tumor formation [52]. The reasons for this seemingly discrepancy may include the dynamic nature of the solid stress, deficient instrumentation for measuring it *in vivo*, and challenges in evaluating its individual biological role amongst complex local phenomena in tumors. Another reason may be that mechanical stresses displace the homeostasis threshold by inhibiting simultaneously proliferation and apoptosis rates, also inducing phenotypic changes.

Besides the mechanical effects that solid stresses exert on the tumor growth and prolifereation, the importance of solid-phase stress in tumors can be illustrated by exploring its role in normal tissue development and function. The mechanical stress on the cell is perceived and integrated at the molecular level through mechanically responsive sensors that interface with biochemical signaling cascades to elicit a specific cellular response (mechanotransduction). Once mechanical cues have been detected indeed, cells must propagate, amplify the physical cue creating in each of them and translate the signal into either a transient response or a sustained cellular behavior. For instance, force and growth factor receptors can each influence cell growth, survival, differentiation, shape and gene expression by regulating the activity of RhoGTPases that, in turn, modulate actomyosin contractility and actin dynamics [41,32,33,40,65,24,74, 100]. Another example of mechanotransducer are integrins which interact with the extracellular matrix (ECM) [42,51]. They regulate integrin-dependent extracellular-signal regulated kinase (Erk), that is involved in cell motility affecting the capability of the cells to interact with the environment through the assembly of focal adhesion [62,95,64]. All these evidences show how the cells respond actively to solid stresses altering biochemical pathways and finally remodeling the cytoskeleton. Not only the cells inside the tumor answer to mechanical stresses but also cells in the stroma. For desmoplastic tumors, the immune system directs the fibroblasts towards the vicinity of the tumor. Under mechanical compression, they become more active in collagen production, increasing the stiffness of the stroma. Eventually these stresses generate a phenotype transformation, passive fibroblasts becoming active myo-fibroblasts with contractile properties [60].

2.1 Role of solid stresses impeding cancer progression

2.1.1 Stress induced by the tissue

Non-fluid–related pressure effects are less studied than the fluid-related ones, as currently no model exists for applying *in vitro* solid stress at *in vivo*-relevant levels, neither any experimental setup *in vitro* may reproduce the heterogeneity that stromal cells display in adult tissues. However *in vitro* experiments offer the advantage of characterizing quantitatively the stress exerted at the cell level and the corresponding long-term dynamics of cell populations. Secondly, some *in vivo* situations may turn to be very close to those *in vitro* experiments, for instance growth after surgery. Helmlinger *et al.* [48] conducted the first experiment aimed at providing quantitative proof of the solid-phase stress effects exerted by the surrounding matrix on the growing tumor. By embedding tumors cells in an inert matrix, where they formed spheroids, the authors found that human colon carcinoma spheroids can grow to a maximum size of 400 mm (diameter) in 0.5% agarose, but only 50 mm in 1.0% agarose (which is less compliant). This was associated with an increase in cell packing and a decrease in cell proliferation. Therefore, a cell confined by a tissue matrix can only divide if its stiffness exceeds the opposing rigidity of its direct environment. Such inhibition of tumor growth can be reversed by releasing the spheroids from the gel. Moreover, by culturing highly metastatic rat prostate carcinoma AT3 and the low metastatic variant AT2 in the same agarose gel matrix used in ref. [48], in ref. [59] it was shown that the solid stress facilitates the formation of spheroids in the metastatic lines, while the AT2 cells maintained their spheroidal morphology even after stress removal.

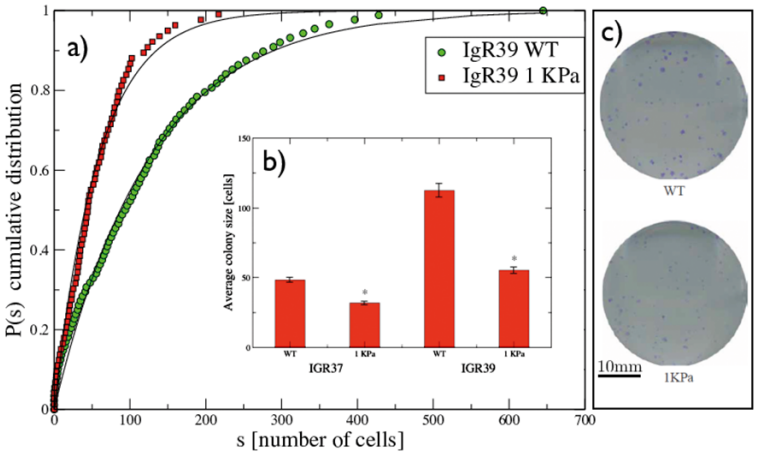

Fig. 1. Effect of osmotic pressure on colony formation in melanoma. a) The cumulative distributions of colony size obtained from IgR39 cells under 1 kPa osmotic pressure with respect to the control (0 kPa). The curves are the fit with a continuous time branching process model (see ref. [6]) yielding a rate division of $\gamma = 0.60$ that is reduced to $\gamma = 0.51$ under osmotic pressure. b) The average value of the colony size distribution with the associated standard error for IgR39 and IgR37 cells. Statistically significant results according to the KS test ($p < 10^{-2}$) are denoted with $*$. c) The images show two representative examples of the colonies for 0 kPa and 1 kPa conditions. Image reprinted from ref. [92].

These observations have raised the interesting possibility that a stiffer matrix can be viewed as a host barrier to tumor invasion, and increasing tissue stiffening could actually impede cancer progression. An hypothesis corroborated by further recent studies with the help of different techniques. In 2009 G. Cheng *et al.* [23] showed that the accumulating solid stress fields in agarose gels around growing tumor spheroids (non-metastatic murine mammary carcinoma 67NR), dictate the shape of the spheroids and suppress cell proliferations, inducing apoptosis in regions of high solid stress.

2.1.2 Osmotic pressure

An alternative method to apply pressure to cell is to use osmotic pressure. Montel *et al.* [67,68] used a dextran solution (a highly biocompatible polymer) to induce a constant pressure on carcinoma cell (CT26) spheroids. While osmotic pressure has a different origin than a mechanical one, the effect is similar: As discussed in 1901 by J. van't Hoff in his Nobel lecture, the osmotic pressure p arises as a result of the collisions of the dissolved molecules with the semi-permeable membrane. In the case of cells, dextran molecules exert a real mechanical pressure on the cell membrane. Hence, there is no fundamental difference with the effect of an equivalent solid stress.

Controlling osmotic pressure allowed the authors of refs. [67,68] to monitor with unprecedented accuracy the actual stress exerted at the cell level, showing that spheroids reached a steady state corresponding to a typical diameter of 900 μm, when the homeostatic balance between the apoptotic core and proliferating rim was established [34,17]. Using a similar method, three of us recently reported results where two melanoma cell lines, primary (IgR39) and metastatic (IgR37), were subject to dextran-induced osmotic pressure [92]. Our results showed that a constant low osmotic pressure affects considerably the proliferation of primary tumors if compared to the corresponding metastatic ones (see fig. 1). The same experimental setup, allowed to study the effect of pressure on cell motility and transmigration capability [61]. The general conclusion is that pressure affects the functional properties of primary tumor cells, but much less those of metastatic cells.

2.2 Role of solid stresses promoting cancer progression

Tumor-associated stroma is composed of several cell types including adipocytes, fibroblasts, and immune cells, as well as a variety of extracellular matrix (ECM) proteins, such as collagen and fibronectin. The onset and advance of cancer leads to distinct changes in the stiffness of the ECM surrounding tissue. Indeed, tumors are often detected as a palpable stiffening of the tissue [50], and approaches such as magnetic resonance imaging elastography and sono-elastography have been developed to exploit this observation to enhance cancer detection [43,39]. More provocatively, altered stromal-epithelial interactions precede and can even contribute to malignant transformation [64], and the desmoplastic stroma that is present in many solid tumors is typically significantly stiffer than normal [74]. What causes the increase in tumor stromal stiffness and how stromal stiffness contributes to tumor progression constitutes central questions in examining tumorigenesis from a mechanical perspective. While the first experimental evidence

that ERK-MAPK signaling acts to regulate Rho and Rac activity and the ensuing cytoskeleton contraction in colon carcinoma cells, thereby playing a major role in cell motility and invasion, was provided in [95], in ref. [73] for the first time it was hypothesized that these cellular biochemical cues could be triggered by compromised tensional homeostasis, *i.e.* by a stiff environment.

High mechanical forces could compromise cell differentiation and alter mechano-responsiveness, thus promoting malignant transformation. However, this is not a one-way process. Cell traction forces generated in the actin cytoskeleton are exerted on these same sites, and thus integrins and focal adhesions are maintained in a state of isometric tension. A rise of cell tension further increases ECM stiffness by tensing or realigning ECM components, thereby creating a deadly, self-sustaining positive feedback loop: cells generate more force, disrupt cell-cell junctions, spread, increase proliferation, and loose acinar organization. Indeed in 2003 Gordon and coworkers [44] used three-dimensional Matrigel-based *in vitro* assay containing $1.0\,\mu$m latex beads, to probe the environment of a dynamically expanding, multicellular brain tumor spheroid. This study presented the evidence that an expanding microscopic tumor system exerts both significant mechanical pressure and significant traction on its microenvironment. In 2005 Paszek *et al.* [74] explored the role of bidirectional force transfer across integrins in the context of differentiation and tumor formation. Using an electromechanical indentor they found that explanted mouse mammary tumors are stiffer than healthy mammary gland. Moreover, culturing normal mammary epithelial cells on ECM gels with varying mechanical compliance, they observed that stiff (force-resisting) ECM gels promote expression of the undifferentiated malignant phenotype, and Rho activity was also higher in these cells. Using both laser-scanning multiphoton and second harmonic generation microscopy, Provenzano *et al.* [76] were able to detect local alterations in collagen density around tumors. Moreover, local cell invasion was found predominantly to be oriented along certain aligned collagen fibers, suggesting that radial alignment of collagen fibers relative to tumors facilitates invasion. Importantly, regions of high breast density were associated with increased stromal collagen [77]. Indeed, an increase in ECM protein concentration, *i.e.* an increased matrix crosslinking or parallel reorientation of matrix fibrils within a stromal matrix, can stiffen a tissue locally to alter cell growth or direct cell migration, albeit to differing degrees.

Some *in vitro* experiments seem to validate this findings. By exerting compressive stress by means of a weighted piston in 2D assays containing mammary epithelial cell lines, Tse *et al.* [55] provided the evidence that the compressive stress accumulated during tumor growth can enable coordinated migration of cancer cells, by stimulating formation of leader cells and enhancing cell-substrate adhesion. More recently, K. Alessandri and coworkers [1] developed a new method based on the encapsulation and growth of cells inside permeable, elastic, hollow microspheres. These confining conditions are observed to increase the cellular density and affect the cellular organization of the spheroid, while, performing invasion assays in a collagen matrix, the peripheral cells readily escape preconfined spheroids. These results suggest that mechanical cues from the surrounding microenvironment may trigger cell invasion from a growing tumor.

At the single cell level malignant transformation may cause also cell softening for small deformations. This has been shown for cell lines [63,46] and tumor tissues [26,79]. The distribution of optical deformability of breast tumors shows a distinct shift towards softer cells with respect to normal mammary tissue obtained from surgical breast reductions [35]. This shift can be attributed to the fact that the prominent fibrous actin of the interphase cell disappears and is replaced by a diffuse distribution of actin [85]. However, at large strains cytoskeletal filaments inherently strain-harden, compensating for the weak linear elastic strength of the actin cortex [56]. It has been argued that intermediate filaments such as vimentin could be the right candidate to support the pressure against the surrounding stroma generated by division and dynamics [22]. This intracellular softening of the cytoskeletal apparatus has been largely overlooked by the biophysical community, although its prominent role for the homeostatic balance has to be established or is violated in spheroids or other malignant phenotypes.

2.3 Mechanotransduction

As the links between stromal collagen density, matrix stiffness, and tumor progression become clearer, the underlying molecular mechanisms are slowly unraveling. In ref. [97] it has been shown that the growth factor TGF-β (acting through the cytoplasmic signaling intermediate Smad3) and the mechanical properties of the underlying matrix play particularly important roles in hepatic stellate cell transdifferentiation, which is the primary cause of liver fibrosis. On the other side, ref. [100] demonstrates that mechanical strain, such as that associated with intestinal transit or tumor growth, can be interpreted by cells of preneoplastic colon tissue as a signal to initiate a β-catenin-dependent transcriptional program. In ref. [64] Leventall and colleagues contribute further insights by establishing a correlation between collagen crosslinking and matrix stiffness *in vivo* and by implicating the ECM-crosslinking enzyme lysyl oxidase (LOX) as a culprit driving stiffness-associated tumor progression. In 2010 Demou [27] introduced two novel systems, the cell-pressors, to enable molecular analyses and live imaging of 3D cell cultures under compression. This study demonstrates for the first time that normal loading could regulate expression of genes involved in ECM degradation, cell-cell contact, migration, and proliferation. The effect of osmotic pressure on the activity of MAPKs and on signal transduction via the RTK PDGF receptor, which plays an important role in cell proliferation, cell survival, cell migration, and tissue homeostasis, has been reported in [71].

3 Interstitial fluid pressure

The vessel wall reacts to multiple chemical and mechanical stimuli in the flowing blood; the mechanical factors are principally pressure and shear stress. These responses often function in a feedback manner either to control blood flow or adapt the vessel structure to its required function. Interest in shear stress biology of cancer cells is principally directed to two related objectives: i) understanding the function of shear in integrated vascular physiology, particularly in resistance vessels and arterial remodeling; ii) a detailed understanding of the cellular mechanisms by which shear stress influences cancer growth, within a mechanotransduction perspective.

Cells require oxygen and other nutrients for their survival and growth. Exchange of gas, nutrients, and metabolites over the capillary wall satisfies these requirements and maintains normal tissue homeostasis. Likewise, cells undergoing neoplastic transformation depend on nearby capillaries for growth. However these vessels are considerably different than normal both in structure and function. The normal blood vessels form a well-organized architecture consisting of arterioles, capillaries, and venules [36]. In contrast, tumor vessels are dilated, saccular, tortuous, and disorganized in their patterns of interconnection [53]. Normal vasculature is characterized by dichotomous branching, but tumor vasculature is unorganized and can present trifurcations and branches with uneven diameters. Perivascular cells in tumor vessels have abnormal morphology and heterogeneous association with vessels [66]. Briefly speaking, the hierarchical organization of the normal vasculature into an arterio-venous architecture is completely missing in tumor vasculature [98]. Moreover abnormalities in both vasculature and viscosity increase the resistance to blood flow in tumors. As a result, overall perfusion rates (blood flow rate per unit volume) in tumors are lower than in many normal tissues. Tumor blood flow is also unevenly distributed, fluctuates with time and can even reverse its direction in some vessels. In addition blood and lymph vessels vehicle metastatic cells and little is known about the first steps of intravasion [12].

Unlike normal tissues, in which the interstitial fluid pressure (IFP) is around 0 mmHg, both animal and human tumors exhibit interstitial hypertension [54]. Two major mechanisms contribute to interstitial hypertension in tumors. In normal tissues, the lymphatics maintain fluid homeostasis; thus, the lack of functional lymphatics in tumors is a key contributor, as drainage of excess fluid from the tumor interstitium is impaired. The net result is accumulation of fluid and, hence, increased fluid pressure in the interstitial space. Indeed, Di Resta *et al.* [28] were able to lower the IFP by placing artificial lymphatics in tumors. The second contributor is the high permeability of tumor vessels. The tumor interstitial fluid pressure begins to increase as soon as the host vessels become leaky, this increases the hydrostatic pressure in the tumor vessels and drives the flow of fluid from the vascular to the interstitial space. Thus, the interstitial fluid may ooze out of the tumor into the surrounding normal tissue, carrying away the chemoterapic drug with it [70,47,9,83]. This findings have been confirmed also by computational continuum models [101,99]. On the other hand, also the reverse situation can arise: when the local IFP overcomes the pressure inside the vessels indeed, the blood flows from the interstitial space into the leaky vessels. In general, however, this can occur only locally, as an IFP higher than the hydrostatic intravascular blood pressure is not sustainable. IFP indeed has been shown to go up and down with the microvascular pressure within seconds [69]. Furthermore, IFP has been found to be nearly uniform throughout a tumor and drops precipitously in the tumor margin [81,13].

Lastly, collapsed lymphatic and blood vessels contribute to elevated IFP in tumors and not the other way around [14, 45,72,48]. Therefore, solid stress cannot be affected by IFP [89] nor the opposite is true, but they can, on the other side cause compression of fragile blood vessels, resulting in poor perfusion and hypoxia [89,90]. Elevated compressive solid stress in the interior of the tumor indeed, 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. Notice that vessel can also collapse due to other mechanisms [49].

4 Computational models

Several computational models for the cancer growth single-cell-based or based on continuum mechanics have been substantiated these experimental evidences [15]. In ref. [21] the tumor was simulated as a two-phase material growing in a poroelastic medium: as the stiffness of the gel was increased, the tumor's growth rate and equilibrium size decreased. Individual-cell models for three-dimensional tumor spheroids growth observed transition from exponential to sub-exponential growth at sufficiently large tumor sizes [30,86,29]. However this is strongly dependent on the interaction involved in the model. Different scaling laws with a linearly time-dependent radius have been obtained [11,10] when in addition to exterior stresses, a cell-cell interaction is introduced. It induces tumor inhomogeneity with a necrotic core, a quiescent zone and a proliferation zone localized at the tumor border. The border velocity is then given simply by the border proliferation rate times the thickness of the proliferative zone. In general the growth of the cell population diameter and of the proliferation pattern can be largely explained by a form of contact inhibition, controlled by a pressure threshold, above which the cell either enters the apoptosis or becomes quiescent [30,29,11]. The use of continuum equations coupled with a poroelastic description of the surrounding medium led the authors of the study in ref. [82] to conclude that the tumor cell size is reduced by solid stress inside the tumor spheroid. Moreover, a continuum description of tissue dynamics, which describes the stress distribution and the cell flow field on large scales, was able to predict that a homeostatic state, encompassing the balance between cell division and apoptosis, was reached in fixed volume [78].

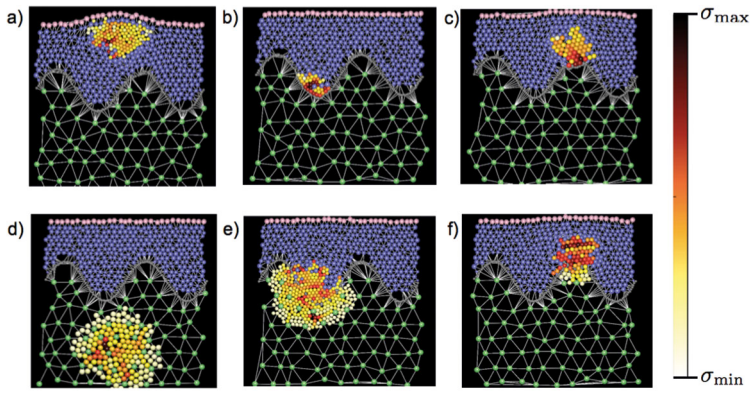

Fig. 2. Morphology of nevi for different locations of the initiating cell for random growth. Illustration of the results of numerical simulations for nevi grown from melanocytes located in different positions in the skin and for different mechanical properties of the basal membrane. Growing melanocytes are shown with a varying color that reflects their compressive stresses σ according to the color bar. a) Nevi grown from melanocytes residing inside the epidermis tend to grow horizontally and do not spread towards the basal membrane. b) Nevi grown on the minima of a strong basal membrane tend to grow roughly parallel to the membrane itself. c) Nevi growing from the maxima of a strong basal membrane tend to grow vertically in the epidermis. d) Dermal nevi tend to have radial shape. When the basal membrane is weak, e) nevi growing from the minima of the basal membrane invade the dermis in a radial fashion, while f) when they start from maxima of the basal membrane the invasion of the dermis occurs more vertically. Image reprinted from ref. [92].

In refs. [67,68,7,75], a mesoscopic model could capture qualitatively the results of tumor growth in dextran solutions, showing that, with a minimum number of hypotheses, cell division may occur only at the spheroid surface while the core is apoptotic, thus yielding a surprising negative homeostatic pressure [75]. In ref. [78] a continuum description of tissue dynamics was developed, describing the stress distribution and the cell flow field on large scales. If the system is confined in a fixed volume, it reaches a homeostatic state in which division and apoptosis balance. Numerical simulations based on a phenomenological continuum theory [96] confirmed that stiff hosting tissues can inhibit tumor growth. The same results have been reached through a single-cell-based model where we have shown that the elastic properties of the surrounding tissue, and its progression to the malignant phase (melanoma) depends on the solid stress exerted by the stromal-cell interactions (see fig. 2) [92]. However not only exterior stresses modify the dynamics of *in vivo* solid tumors but also the morphology of host tissues. Indeed most of solid tumors originate from an epithelium which covers the inside walls of organs. For skin tumors and more precisely melanomas, the avascular phase occurs in the epidermis, a thin layer which varies in our body from 0.1 to 1 mm, giving rather a disc shape than a spheroid and strongly modifying the transport of nutrients inside the tumor. Since melanoma observations are part of the diagnosis, a more realistic continuous modeling introducing the exterior stresses, the cell-cell interaction but also the basal geometry [3,4] allows to recover the phase segregation between the cancerous melanocytes and the healthy keratinocytes observed in melanomas (also detected by dermatologists) and some specific melanoma shapes occurring in palms and soles *in situ* (see figs. 3 and 4) revealing the tumor growth sensitivity to confinement.

Continuum and individual-based computational models have often focused on the mechanical stress that the stroma opposes to the tumor invasion, arguing that this mechanical stress may be the key to regulate the cancer growth, dictating the progression to a malignant and metastatic phase [8,18,7] (see the reviews in refs. [16,2,93,87, 80] for an account on the progresses in mathematical modeling of cancer over the past 50 years). Using a continuum hydrodynamic description of tissues, in [7] several biological questions including the origin of metastatic inefficiency [8] and fingering instabilities [11] frequently observed at the stromal-epithelial interface [7,25,4] were addressed. In ref. [18] a spatially independent system of non-linear ordinary differential equations was explicitly solved in some cases of biological interest, showing a first phase in which some abnormal cells replace the normal ones, a second phase in which the hyper-proliferation of the abnormal cells causes a progressive compression within the tissue itself and a third phase in which the tissue reaches a compressed state, which exert pressure on the surrounding environment. At the same time single-cell-based simulation studies cover the growth behavior of epithelial cell populations, ranging from undifferentiated stem cell populations via transformed variants up to tumor cell lines [20,31,37,38].

5 Conclusions and perspectives

In vitro experimental model systems have been studied in the last few years with the aim to understand the role of solid stresses. They give important insights on the transformation of cell behavior under external forces, especially on the proliferation rates. However these models misrepresent the complexity of primary tumors, especially the vascularized ones. Due to angiogenesis, the vascularization inside the tumor occurs with an interplay between the solid stresses

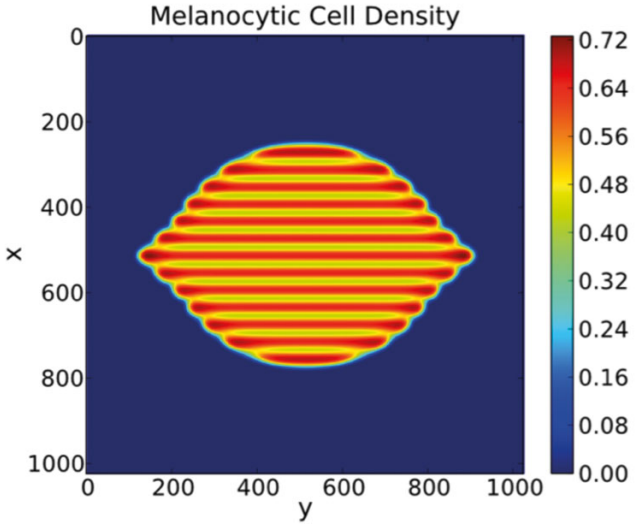

Fig. 3. Final morphology of nevi occurring in palms and soles. These nevi and melanocytes arise in thick epidermis where the basement membrane has pronounced waviness at the origin of our fingerprints. The simulations are based on the mixture model with cell-cell interaction and outer border pressure, treated in 3D with lubrication approximation. The flux of nutrients coming from the dermis diffuses in the whole thickness of the tumor. It is also treated in 3D with lubrication approximation. The averaged melanocyte concentration follows the stripe orientation of the basement membrane but the maximal value of concentration depends on the location of the cancerous cells originated from the basement membrane. Image reprinted from ref. [3].

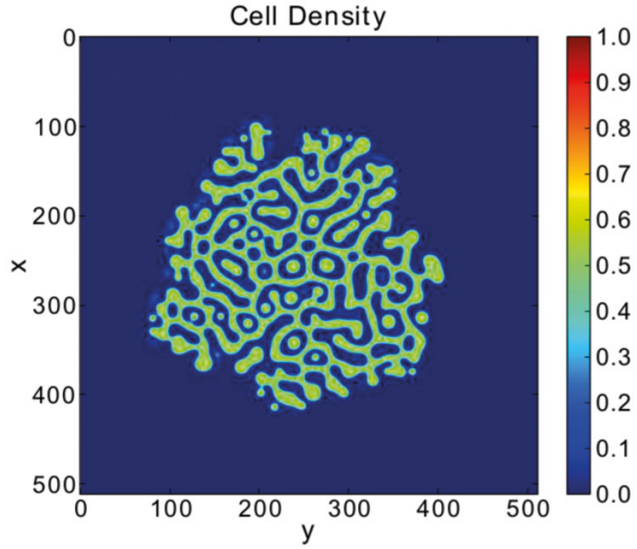

Fig. 4. Final heterogenous morphology of melanocytes. Typically melanoma observations with dermoscopy exhibit color inhomogeneity due to aggregates of cancerous melanocytes. These aggregates are due to the E-cadherin switch at the origin of the cancer. For healthy skin, melanocytes avoid each other, this is not the case when the pathology appears. To represent this attraction, a cell-cell interaction is introduced leading to a spinodal decomposition in the simulations and in the tumors. At intermediate time scales, one can notice "theques" and "nests", in the simulations (according to the clinical diagnosis nomenclature). This heterogeneity is one of the criteria for identification of a melanoma *versus* a nevus. Image reprinted from ref. [4].

and fluid pressure, changing the nutrient transport properties and modifying the tumor morphology although these cannot directly affect each other. Indeed, the lymphatics cannot penetrate, but the vessels can be found in close vicinity, participating in the stroma transformation and in the escape and metastasis of tumor cells [58]. In addition, for desmo-plastic tumors the stroma becomes stiffer and stiffer, also participating in the solid stresses, not only as an environmental obstacle but because it contains active cells originated from the immune system which contribute to this high level of stresses. Fibroblasts and myofibroblasts have been detected in the stroma of many carcinomas, during E-M-T transition. There is no doubt that stresses change the cell phenotype during all the metastasis voyage and their mechanical properties [94]. Not only are shear fluid stresses important in the vasculature, but also cancer cells of diameter $20\,\mu$m have to pass through capillaries of lungs for example of order $8\,\mu$m proving their excessive adaptation.

Mechanical stresses, active or passive, are part of the diagnosis, palpation of the breast and the first sentinel node being an alert for tumor breast but also melanomas and the stiffness difference between the tumor and the environmental tissues is used in sensitive detection by surface ultrasonic elastography techniques [57]. Such study on tissues properties in cancero-genesis will allow to understand the poor results of chemotherapy and nano-particles treatments, especially in the case of desmoplastic tumors as shown recently in [19]. Indeed nano-medicine and chemotherapy strategies are not so promising because of the abnormality of the stroma combined with the heterogeneous structure of the tumor and the blood flow distribution. To overcome the large number of barriers, physical and biological, and normalize the stroma in all aspects will be a promising axis for the future.

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