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Review

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Spatial confinement and life under pressure from physiology to pathology

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Tree roots sprouting into the ground or tumors proliferating within an organ are a few examples of proliferation under spatial confinement, which leads to growth-induced pressure. This compressive mechanical stress can impact a plethora of processes in all organisms. In this review, I will discuss the physiological and pathological consequences of spatial confinement in plants, microbes and animal cells, and will discuss in more depth the case of solid tumors.

Cells live in spatially-confined environments—this is often more the rule than the exception. Spatial confinement can be total, like roots sprouting into the porous soil, or partial, like cell growth on a substrate. When cells proliferate in confinement, their growth leads to the emergence of a self-inflicted mechanical compressive stress, which we will refer to as growth-induced pressure (GIP) (Fig. 1). GIP is a mechanical pressure and is not to be confused with osmotic or hydrostatic pressures—although it could share some similarities with the former[1,2], and the latter has been recently implicated during development[3]. In this review, we will discuss both the physiological and pathological effects of confined growth and subsequent GIP, in all living kingdoms, from plants to fungi and bacteria, all the way to animal cells.

The effect of GIP has been much less studied than the effect of tensile stress, probably due to methodological limitations to confine cells. Moreover, the effect of tensile stress is largely restricted to animal cells, due to their contractile cortex[4], which most walled-organisms do not possess. Recent experiments suggest that GIP can impact a myriad of processes in cells, ranging from cell growth and division to cell apoptosis, cell migration, or cell (trans-)differentiation. The topic being broad, this minireview is not meant to discuss all the results of the field but to rather illustrate the problematics of GIP. I will not discuss in this review the different means to confine cells and study GIP, which mainly rely on hydrogel embedding and microsystem confining chambers. Additionally, I will not discuss the effect of spatial confinement on cell motility. There are excellent reviews (see, for instance, ref. 5) on the effect of confinement in cell migration, which is restricted to mobile animal cells.

Growth-induced pressure is a natural component of physiology in all kingdoms

Plant development is a great example of how cells can be totally or partially confined. For instance, tree roots naturally expand in the soil, and are totally confined in this dense and porous environment[6]. It has been shown that plant cells are able to develop a large mechanical stress, in the MPa range (tens of atmosphere)[6], enough to break GPa concrete. GIP generated by plants, but also by microbes, thus participates in biodeterioration[7]. However, cells are confined in 2D and not in 3D at the surface of the tip of the plant, thus being partially and not totally confined. The aerial tip of *Arabidopsis thaliana* is an interesting example of the link between GIP and organogenesis[8]. Localized outgrowth at the periphery of the shoot apical meristem leads to the buildup of planar GIP, which is evidenced by nuclear compaction at the interface between the growing organ and the meristem. The histones of the cells in this region are further methylated[8] by this mechanical compression, and their proliferation seems stalled[9], determining the boundary of the nascent organ. These data show that GIP is an essential component of plant organogenesis.

Microbes, too, can develop in the soil and in porous environments[10,11]. Natural confinement and compression can also occur inside our body, in the gut notably where food can generate polyelectrolytes that lead to the swelling of the mucus and the compression of potentially embedded microbes[12]. Bacteria and fungi are also developing as colonies called biofilms, where cells are surrounded by other cells and an extrapolymeric substance (EPS). GIP can emerge within these structures, but also as the structure expands on its own: 2D bacterial colonies growth with no substrate adhesion but displaying large friction leads to the buildup of GIP. This compression shapes the folds of the colony[13] and has also been associated with EPS production. This local compression leads to confined bacterial cell death, which facilitates 3D growth and the formation of wrinkles[14]. In addition, GIP has been shown to decrease cell proliferation in both fungi[1,15,16] and bacteria[17,18]. In *Pseudomonas aeruginosa*, cell compression activates cAMP, leading to cell growth regulation, as a potential means to gauge population density[19]. As such, compressive stress, by modulating different traits of the population—division, cell death, ECM production—is an essential component shaping microbial colonies[20].

Spatial confinement can be found both in 2D and 3D in the case of adherent animal cells. When cells proliferate on a 2D substrate, they start, just like microbes and plants, to build up a planar compressive stress[21]. In two-dimensional in vitro systems, this compressive stress has mainly been studied in the framework of the so-called contact inhibition[22]: when cell density gets too high, cells start to regulate their number by acting on both cell division[21] and cell death[23,24]. However, what they mechanically

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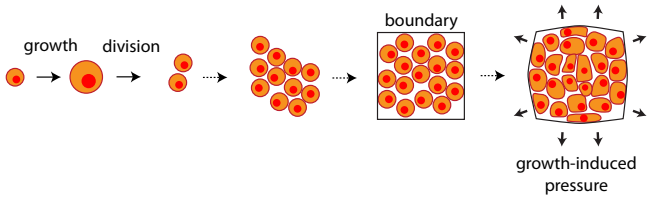

Fig. 1 | Cells proliferate in a spatially-confined environment. This confinement can be total or partial, and can lead to the emergence of growth-induced pressure, which compresses both the surroundings and the cells. Growth-induced pressure has physiological and pathological consequences in all realms of the living.

experience in the bulk is a compressive GIP. Stretching a dense monolayer leads to cell cycle re-entry[25], while further compressing it just stops cell proliferation[26]. Similarly to microbes, local hotspots of compression are correlated with cell extrusion[27], ensuring a constant cell density in monolayers. However, a cell's ability to contract (pull) or extend (push) within a monolayer seems to depend on a tight balance between intercellular and intracellular forces, mediated in part by E-cadherins, such that a monolayer of fibroblasts would be under tension while a monolayer of epithelial cells would mainly be under compression[28]. This different sensitivity could be essential when it comes to cells mechanically competing for space[23].

The emergence of planar GIP is also found in the context of animal organogenesis. During the development of the leg of the fruit fly *Drosophila melanogaster*, cells are under a natural compression, which is exerted by the surrounding tissue and the confining peripodial envelop. This compression is essential to morphogenesis, as it promotes local cell extrusion, leading to apical pulling forces, and generating the future folds of the leg[29]. Apoptosis is preferentially localized in the future fold and is induced by compression, as the removal of the envelop and relaxation of natural compression dramatically reduces the number of cell death events, while increased compression does the inverse. As such, similarly to microbes, compression is essential to the shaping of folds. Interestingly, spatial confinement, among other factors, also seems to be implicated in cortical folding[30,31], which is essential for the proper functioning of the brain.

Three-dimensional confinement is equally present during organogenesis, as recently exemplified during rodent incisor development[32]. Local 3D cell proliferation leads to the emergence of growth-induced pressure, which locally deforms nuclei, similar to what has been shown during plant organogenesis[8]. Cell proliferation is shown to be progressively inhibited in the region of compression, which is known to regulate the gene expression of a specific cell cluster within the dental organ, called the enamel knot. Proliferation-induced mechanical compression, which is possible through the confinement imposed by the surrounding tissue, thus drives the formation of a signaling center that organizes tooth formation, regulating both cell proliferation and cell fate.

Ultimately, growth-induced pressure emerges as a natural component of physiology across all living kingdoms. It plays a crucial role in shaping and maintaining plant/animal organs or microbial colonies. In particular, local confinement and growth-induced pressure can be an integral part of signaling centers which are essential during organogenesis and could be superimposed to or even at the origin of chemical signals. The shaping of organs or colonies is facilitated through the mechanical regulation of ECM or EPS production, alongside the control of cell division, cell death, and cell fate. Compression resulting from local confinement also seems important for homeostasis, by for instance maintaining confined oocytes into dormancy[33] or muscle stem cells[34] into quiescence.

Pathological aspects of cell confinement

Pathogens could locally compress host cells, and similarly, modifications of the local mechanical environment can prime host cells to be resistant to their natural pathogens. Recently, interaction between plants and micro-organisms has been proposed to involve mechanical forces and to potentiate mechanoperception[35]. It has been shown that the lysing action of the fungus *Sclerotinia sclerotiorum* leads to locally decreased mechanical stress, releasing cell-wall-born tension. This triggers distal cell mechanical perception of this injury and reorganization of the mechanosensing cortical microtubules, which are required to regulate immunity-related genes. This mechanism of mechano-signaling triggered immunity could complement the classical molecular signaling involved in plants' response to pathogens.

Microbes can be naturally compressed within their environment, either when proliferating in microcolonies, when occluding blood vessels[36], or when invading the mucus. *Escherichia coli* compression has been shown to increase the Rcs (regulator of capsule synthesis) phosphorelay pathway[17,37], the envelope stress response pathway, resulting in the production of an extracellular capsule. Through the development of clever microfluidic devices, the authors have shown that compression induces persistent *E. coli* growth in the presence of T7 bacteriophages, even at high concentrations of phages[37]. Interestingly, T7 bacteriophage resistance occurred at a frequency much higher than what would be expected from the selection of resistant mutants, suggesting that mechanical compression truly primed this high degree of resistance. Similarly, resistance to antibiotics has been found during the confined growth of *E. coli* and *S. aureus* in human ECM of physiological rigidities[38]. Resistance has been associated with a downregulation of TCA cycle, improving antibiotic resistance, but could also be associated with Rcs regulation.

Growth-induced pressure could also emerge during intracellular pathogens growth, such as uropathogenic *E. coli*. *E. coli* cells proliferating in confinement and developing GIP have been shown to uncouple growth and division, thus leading to the formation of very small cells, such as the ones usually found during UPEC infections[17]. This strategy of mechanical stress buildup during intracellular confined growth could be a common mechanism of infection for multiple microbes.

Besides host-pathogen mechanical interaction, or mechanical compression priming specific resistance, cells within confined space must undergo tightly-regulated cell proliferation and differentiation during development or in homeostatic conditions. Abnormal local growth during development or in an adult stage can lead to disorders, like anomalous spatial confinement of neural crest cells which seem to contribute to craniofacial abnormalities and other congenital conditions[39]. Another famous example of abnormal local growth is the case of solid tumors. Pioneering work from the group of R.K. Jain established that tumor proliferation leads to the storage of solid stresses and in particular compressive stress[40–42]. This compressive stress can have various origins, one coming from the local cell proliferation, in the form of GIP, and another coming from excessive ECM deposition, in particular the highly negatively-charged hyaluronan which can swell due to the repulsive forces from these negative charges[43], further compressing the tumor. Moreover, the rigidification of the stroma leads to stronger cell confinement and GIP generation[44].

Compressive stress within tumors has a large number of consequences, both for the tumor cells, but also for the stromal compartment. As has repeatedly been shown in multiple organisms, cell proliferation in all living kingdoms is dramatically impacted by confined growth and GIP (see Box 1 below). Apart from one study[45], to my knowledge, 3D confined growth does not seem to have a large impact on cell death. This is perhaps not surprising: while in 2D cells can extrude from the tissue, extrusion is not possible within a tight 3D environment. One major potential consequence of this proliferation decay under compression is chemotherapeutics resistance[46]. It has been shown in vitro that confinement-induced cell proliferation reduction directly limits the number of target cells for classical chemotherapy drugs such as gemcitabine (targeting cells during DNA synthesis) or docetaxel (targeting cells during mitosis), thereby participating in a mechanical form of drug resistance.

The stroma is equally impacted by this compressive stress. One major effect of mechanical compression is the collapse of blood vessels[47]. This decreases tumor perfusion, leading to lower accessibility to drugs, and to any other blood-injected material. Means to decompress the tumor to increase accessibility are currently under clinical trial, such as

Box 1 | Modulation of cell proliferation under GIP

Currently, it is not clear how GIP modulates cell growth and cell division, but both seem to decrease under GIP in all studied organisms. The coordination of cell growth and division also seems lost, as it has recently been shown that both *E. coli*[17] and mammalian cells[60] become extra-small after a round of cell division at almost fixed volume, which does not seem to be the case in *S. cerevisiae*[1]. While in animal cells some key players have been identified as likely co-modulators of confined cell division, such as YAP/TAZ[50] and Piezo[25], or CDK inhibitors like p21[44] and p27[61], the sensing of this mechanical compression is not elucidated. In fungi, pathways have been identified which can modulate both cell survival and cell division[16]. A feature that seems conserved to the emergence of GIP is the increase in macromolecular crowding[1,17,62] which, together or alone, could modulate cell proliferation[2]. Together, the changes in both the cellular physical properties and of unknown signaling pathways seem key to coordinate a decrease in growth and division under confinement.

the use of hyaluronidase[48] which seems to decompress blood vessels in mice[47]. Cells within the stroma can also be impacted by this mechanical compression. In vitro, it has been shown that fibroblasts can be activated into cancer-associated fibroblasts (CAFs) by compression[49]. A recent study has shown that CAFs are able to surround and compress multicellular spheroids in vitro, leading to decreased cell proliferation[50]. In vivo, they are also found to surround the tumor which seems compartmentalized into small clusters, which are enriched at their borders in these highly contractile CAFs. These results suggest a mechanism in which CAFs seem to naturally control tumor progression through mechanical compression.

Concluding remarks: pressing down on tumors?

Cells are confined by their environment, either partially in two dimensions or totally in three dimensions. Confinement is found in both physiological and pathological conditions: during the normal development of plants, fungi, bacteria, or animals, but also in the life cycle of pathogens which can generate compressive stresses. Oftentimes, the pathological interaction with a host cell resembles the physiological response of this cell to mechanical stress: abiotically mechanically stressing cells, for instance, leads to resistance to some natural pathogens[51], which, during their infection, may be exerting similar biotic mechanical stresses.

Tumor growth is a great example where the pathology naturally meets the physiology, and where mechanical compression could be important both in cancer initiation and treatment. In a seminal review in 2011, Bissell and Hines asked the following question: "Why don't we get more cancers?"[52]. They proposed that the microenvironment could be restraining cancer progression. Our recent knowledge on the matter suggests that part of this restraint could be mechanical. While abnormally proliferating cells would generate solid stress, this stress could physiologically activate distal fibroblast[49], which could control the microtumor mechanically by compressing it[50], without being able to close this "wound that does not heal[53]", but preventing further growth. In the XVIIIth century, French clinician Joseph Récamier studied the effect of a soft compression on breast clumps—at the time, it was hard to know if these were real tumors, and found interesting results, showing decrease or control of the growth of clumps[54]. At the same time, it seems that too much pressure could lead to quicker patient death[54], and recent results imply that, on top of compressing blood vessels[47], potentially increasing drug resistance[46], compression seems to also promote cell migration[55–57] and favor tumor development[58,59], suggesting that maybe, in some cases, mechanical pressure should be decreased. *Release the pressure* in the tumor, or put it *under pressure*, will depend on the type of tumor, and will require much more investigation before being used as a therapeutic solution.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

M.D. wrote the manuscript.

Competing interests

The author declares no competing interests.

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