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Review

The first embryo, the origin of cancer and animal phylogeny. V. Cancer stem cells as the unifying biomechanical principle between embryology and oncology

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ABSTRACT

The role of embryology in metazoan evolution is rooted deeply in the history of science. Viewing Neoplasia as an evolutionary engine provides a scientific basis for reexamining the disease cancer. Once the embryo is understood as a benign tumor with a pivotal role in the evolution of all animal forms, there will be an immediate paradigm shift in the search for cancer cure, potentially revealing insights that may be buried within the great developmental transitions of metazoans. This article discusses one of the unifying principles between embryology and oncology, namely cancer stem cells. Some considerations are also provided on the central role of physics and biomechanics in the assembly of the first embryo, which can be regarded as a differentiated benign tumor. Mechanical impregnation of the nucleus of a stem cell, culminating in a totipotent/multipotent cell, was a major event safeguarding the success of embryogenesis throughout evolution. Germ cells in the earliest ctenophore embryos underwent delayed differentiation, subsequent to the mechanical assembly of the embryo. Finally, a discussion is presented on the concept that cancer and embryogenesis (cancer and healthy stem cells) are two sides of the same coin, that is, of the same process. The only difference is that cancer stem cells reveal themselves in inappropriate contexts. Neoplasia is a free force, whereas cancer is a force contained by animal organization.

1. Introduction

For an embryo to develop, cells must be capable of proliferating in a physically united manner, in addition to performing early mechanical phenomena such as fertilization. The theoretical framework of this article is based on a unique and innovative perspective on animal evolution, wherein embryonic multicellularity and embryogenesis are understood as neoplastic processes[1] (see Box 1). After fertilization and mitotic division of the zygote, the first animal cells "learned" to stick together connected by cadherins. With epiboly, cells learned to migrate together, representing the first great revolution in animal history[2] (see Fig. 1A and B and Box 1). Cancer cells also manifest the distinctive ability of collective migration. In the case of cancer, loss of the restrictions imposed by cadherins unveils the expansive and transforming force that is at the root of animal genesis. Neoplasia is not simply cell proliferation but rather a transformative force. Here, Neoplasia is referred to as the neoplastic process, a cellular mechanism that represents the beginning of the phylogenetic and evolutionary trajectory of animals.

The advent of the extracellular matrix (ECM) marked the onset of a new phase for embryogenesis. Embryonic cells began to assemble and remodel the basal lamina. This had profound implications for the diversification of structural changes and the creation of new animal forms. For example, by remodeling the basal lamina, cells initiated epithelial–mesenchymal transition (EMT) and projected into the mesoglea. The development of this ability represents the second major revolution in metazoan history.[2] During EMT, amoeboid movements acquired from our protozoan ancestors[3,4] manifested themselves into an invasive ability to explore new compartments during embryogenesis. On the other hand, this metastasis-like movement of mesenchymal cells is controlled by the differentiation dynamics of the embryo, denoting that the neoplastic force is repressed by embryonic organization. Furthermore, the remodeling of the basal lamina created new compartments, exponentially multiplying the potential for new forms and interactions within the embryo.

Next, we will unravel which biomechanical forces (herein also referred to as neoplastic forces) operate in embryogenesis, in line with my proposal that the embryo would be a differentiated benign tumor (see Box 1).

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Box 1. Glossary of the founding principles of this study's hypothesis.

Embryo: a differentiated benign tumor that is nourished and protected by macrophages and endowed with the ability to form germ cells, which are impregnated with mechanical memory to recreate the process of embryo development in the next generation.

Neoplasia: the driving force of evolution, fundamentally governed by biomechanics. It is characterized by the normal, continuous, and collaborative growth of embryonic cells, which develop together to form tissue structures and shape the embryo. Neoplasia is induced by the fertilization of an animal oocyte. The disease cancer, the most well-known form of neoplasia, arises when this collaboration between cells is disrupted.

Neoplastic process: a broader concept than neoplasia, the neoplastic process is intrinsic to cellular dynamics and includes both cell–cell interactions and interactions between cells and the extracellular matrix during embryonic morphogenesis. It also encompasses the forces generated by these interactions and how they imprint the cellular genome with mechanical memory. This process unfolds within a specific time frame relative to the ontogeny of animals and has consequences for phylogeny, as the mechanical memory is passed on to subsequent generations, influencing embryo reconstruction and self-renewal ability. Cancer is also a neoplastic cellular process, as cancer stem cells possess the ability to recapitulate the generation of a continuously growing tumor and generate all the heterogeneous lineages that comprise the embryo.

Mechanical memory: Cells have the ability to sense and store a memory of their previous mechanical environment. Stem cells preserve the mechanical memory of the embryo, as well as that of differentiated and compromised cells from any lineage. Among these differentiated cells, the most relevant are germline cells, which use this mechanical memory to rebuild the embryo in the next generation. Thus, when two differentiated cells (germline cells) fuse, a totipotent zygote is formed, capable of reconstructing the biomechanical processes of the previous generation.

Zygote:an embryo in a totipotent one-cell stage that is not a stem cell.

Embryonic history:the physical trajectory of the creation of the first animal form, which is impregnated in the embryo's genome. This trajectory follows the tracks of a neoplastic process. The main cells recording this physical history (totipotency) are the germ cells, and the key record of this trajectory is germline segregation. Any embryonic or adult (somatic) cell that initiates cancer will also express germline genes (soma-to-germline transition), as it recapitulates the neoplastic and physical processes that are part of its historical-evolutionary origin.

Self-renewal:a cell's ability to divide and produce one or more daughter cells that retain the same characteristics as the original cell. All embryonic/neoplastic processes are based on the ability to differentiate while preserving the ability to reproduce or reconstruct the process.

Totipotency: the ability to produce a mature organism. It encompasses the ability to generate all cells of a body and organize them in a specific temporal and spatial sequence, that is, to undergo coordinated development. Totipotency is directly related to a cell's mechanical memory. Thus, a single totipotent cell, or zygote, is a one-cell embryo with the intrinsic ability to initiate and sustain a globally coordinated developmental process.

Germline cells: lineage of stem cells specialized in transferring cellular organization to progeny. They are fundamental for biological organization and the process of animal evolution. Egg and sperm cells are referred to as germ cells, different from the rest of the body's cells, which are known as somatic cells.

Germline segregation: complex process by which germline cells are separated from somatic tissues during development. The production of germline cells from multipotent adult cells in late development, called multi/totipotent adult stem cells, has been observed in basal animals, such as ctenophores, sponges, cnidarians, and flatworms.

Soma-to-germline transformation: a process by which somatic cells acquire characteristics of germline cells. Germline genes are always extensively activated in a wide range of tumors, suggesting that an oncogenic soma-to-germline transformation may be a hallmark of cancer. This hallmark would indicate an intrinsic reproductive characteristic in cancer development.

Germline's reproductive program: term coined by Bruggeman to explain that soma-to-germline transformation is intrinsic to the development of cancer.

Biomechanical forces: any and all force generated during the physical trajectory of embryo development. The extent of mechanical memory is influenced by both the magnitude and duration of mechanical/fluid stress and matrix stiffness.

Atavistic: relating to or characterized by atavism; reverting to, recapitulating, or resembling the characteristics of a remote ancestor or primitive type.

Epiboly: the spreading of cells into sheets of tissues that overlie or surround other groups of cells, as observed in the formation of certain gastrulas.

Stem cell: an undifferentiated cell of a multicellular organism (including embryos) that is capable of indefinitely giving rise to more cells like itself. In other words, stem cells are capable of self-renewal. They may also differentiate into other cells with different functions.

Cancer stem cell: cell within a tumor that has the ability to self-renew and give rise to the different cell types found in cancer. Cancer stem cells can only be defined experimentally by their ability to recapitulate the generation of a continuously growing tumor.

2. Considerations on the biomechanical forces operating in embryos and cancer cells

Embryo formation comprises a series of sequential stages of transformation (e.g., blastula, gastrula, neurula) that give rise to the embryo's shape. This process, called morphogenesis, relies on the control of mechanical properties at both the cell and tissue levels, as well as on highly regulated spatiotemporally controlled forces that act to dynamically remodel tissues.[5] Thus, tissue-scale biomechanics play a crucial role in germ layer rearrangement during embryo morphogenesis.[6]

By adapting force production to material properties, the embryo can facilitate tissue movements,[7,8] triggering collective migratory movements (epiboly and convergent extension) or movements responsible for organizing the three germ layers during cell ingression by EMT in human gastrulation. These mechanical forces are translated into mechanical and fluid stress (see Box 1). For example, fluid stress can be conceptualized by viewing a zebrafish embryo as a spherical-shaped tensile cortex surrounded by a viscous fluid (vitellus).[9] There is also evidence that fluid viscosity influences cell migration.[10,11]

It is well established that cancer cells exhibit processes similar to those seen in embryonic development, such as collective migratory

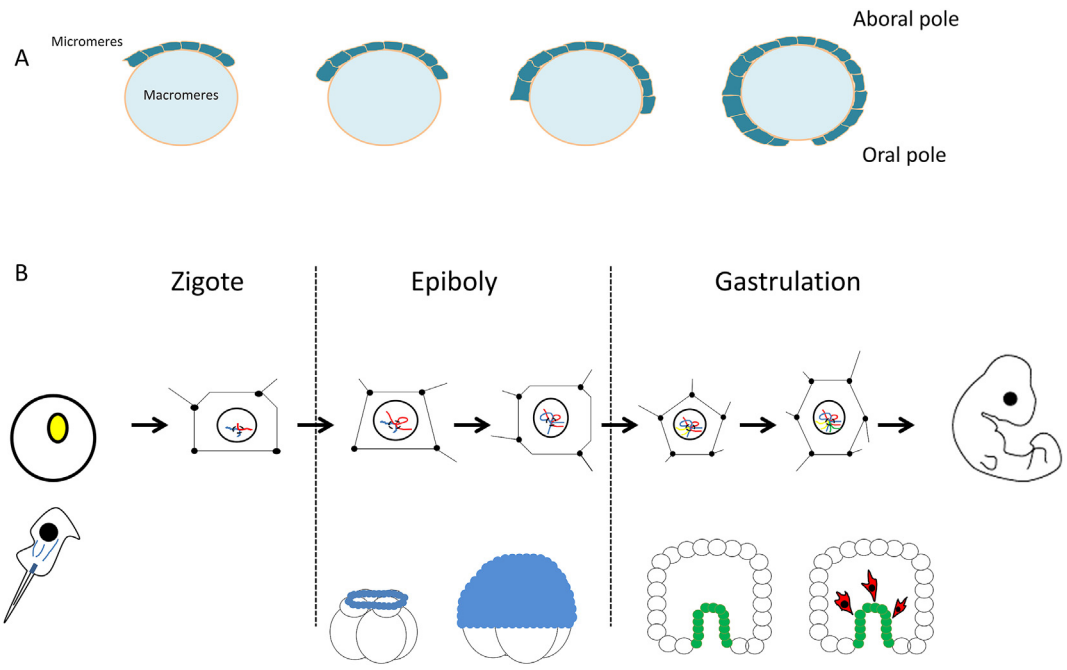

Fig. 1. Early development of Ctenophora. **A.** Schematic of epiboly movements. Micromeres at the aboral pole divide and associate to collectively migrate over macromeres toward the oral pole. During epiboly, the extracellular matrix (ECM) is formed. **B.** General scheme of the neoplastic functional module (NFM). Chromosomal domains in the cell nucleus become topologically associated due to physical impacts occurring during embryo assembly. The projected points and lines of geometric figures represent the impact of embryonic morphogenesis on the cell nucleus. Cells finishing gastrulation are multipotent and receive most of the biophysical impacts that promote embryo patterning. Some of these cells will give rise to germline cells that separate from somatic tissues. This ancestral event takes place in basal animals after morphogenesis, that is, at highly advanced stages, when the embryo shape has already been established. Multipotent cells and germline cells are equipped with mechanical memory and the NFM, elements that contribute to replicating the process in the following generation. The emergence of animal phylogeny, cancer, and the first embryo is implicit in the events represented in this diagram. Considering the development of Ctenophora and the temporal and spatial organization of surface tension and stiffness, my hypothesis suggests that these mechanical factors triggered the formation of the animal body (B, lower panel).

movements[12,13] and mesenchymal–epithelial transition,[14] which are a harbinger of the invasive phenomenon known as metastasis.[15,16] The striking similarity between embryonic development and cancer processes is well-recognized.[17,18] All the similarities between cancer and embryology discussed in this article stem from the proposition that the embryo is a differentiated benign tumor, which forms the basis of this hypothesis about the origin of cancer.

Thus, the scientific literature already contains a theory about the origin of the disease cancer from an embryological perspective.[19] Such a theory, however, fails to contemplate one of the main dimensions that should be included in a contemporary hypothesis, that is, an evolutionary perspective, given that cancer affects all animal groups.[20–27] It should be noted that some theories discuss the origin of cancer from an evolutionary viewpoint,[28,29] but without addressing the embryonic dimension. Offering a unique perspective, the hypothesis presented in this article combines embryonic, atavistic, evolutionary, and, especially, contemporary perspectives incorporating the role of physics in the formation of the first embryo and the origin of cancer.

The physical and mechanical properties shared by cancer and embryonic processes can no longer be dismissed as mere coincidence. As will be shown below, the resolution of these physical parallels will inevitably impact clinical and basic sciences. Understanding mechanical phenomena (the physics of development) and how they have been refined throughout evolution opens a window of opportunity for the study of human oncology and offers the possibility of studying cancer from the perspective of animal phylogeny, tracing its history from the emergence of Ctenophora to humans. The cure for cancer lies in the biophysical clues left by evolution.

The ECM is constructed and increases in stiffness during epiboly, in the early stages of embryogenesis (see Box 1 and Fig. 1). This property, also known as ECM stress, provides the necessary adhesion and mechanical forces for embryo growth. Matrix stiffness is a critical physical factor influencing the embryonic microenvironment. Physical signals induced by matrix stiffness are transmitted to embryonic cells mainly as mechanotransduction stimuli, resulting in changes in embryo cell morphology, increased proliferative capacity, and spatially oriented migratory invasiveness. In the context of embryonic differentiation, stiffness variations are fundamental for regulating the behavior of mesenchymal stem cells.[30] There is a consensus that textural gradients (soft to stiff or stiff to soft) are required for orienting migratory movements (durotaxis) during gastrulation.[31] Also, the force and contractility produced by migrating cells and reorganizing tissues are fundamental for embryonic morphogenesis.[32] In other words, stiffness and contractility are crucial for embryo patterning.[32]

Table 1
Mechanical forces measured in tissues, non-cancer cells and packaged DNA (*in vivo* and *in vitro*).

Source of evidence	Mechanical Force	Unit
Normal tissue or in vitro		
Normal mamary gland	Stromal matrix stiffness	167 ± 31 Pa
Neuron differentiation in vitro	Elasticity (matrix stiffness)	0.1–1 kPa
Muscle differentiaton in vitro	Elasticity (matrix stiffness)	8–17 kPa
Bone differentiation in vitro	Elasticity (matrix stiffness)	25–40 Kpa
DNA compaction		
Cohesin-mediated DNA compaction (completely compacted)	Mechanical force	0.3 pN
Cohesin-mediated DNA compaction (incomplete compacted)	Mechanical force	0.6 pN
Cohesin-mediated DNA compaction (minimal compactation)	Mechanical force	0.8 pN

Table 2
Comparison of forces exerted by animal cancers and embryos.

	Species	Tissue, cell line, or solid tumor	Force	Stress	Migration	Stemness
Cancer	Human	Oral squamous cell carcinoma (SCC25)		10 Pa adhesion strength (20 kPa substrate)	Durotaxis	
		Breast cancer (MDA-MB-231)	$\|F\| = 300$ nN	1.2 kPa traction force (5 kPa substrate)	Reverse durotaxis	
		Human ovarian adenocarcinoma (SKOV3)		2 kPa traction force (stiff substrate, 20 KPa)	Durotaxis	
		Prostate cancer (DU145)		0.5 kPa traction force (12 kPa substrate)		
		Prostate cancer (PC3)	$\|F\| = 200$ nN	0.5–1 kPa traction force (5 kPa substrate)	Durotaxis	
		Metastatic lung adenocarcinoma (A549)	$\|F\| = 150$ nN	0.6 kPa traction force (5 kPa substrate)	Durotaxis	
		Cervical adenocarcinoma tumor (Hep-2)			Reverse durotaxis	Softness induced stemness
		Human osteosarcoma (U2-OS and MG-63)				Softness induced stemness
		Human hepatocellular carcinoma (Huh7)			Durotaxis	Softness induced stemness
		Human hepatocellular carcinoma (Hep3B)			Durotaxis	Softness induced stemness
		Glioblastoma (U87)			Reverse durotaxis	
		Glioblastoma (T98G)			Reverse durotaxis	
		Mesenchymal fibrosarcoma (HT1080)			Reverse durotaxis	
		Breast cancer (solid tumor) Pancreatic cancer (solid tumor)		5–20 kPa, >5 kPa in the invasive front Increased strain ratio		
	Mouse	Melanoma (B16–F1)		0.12 kPa traction force (0.6 kPa substrate)		Softness induced stemness
		Premalignant basal cell carcinoma (solid tumor)		7 kPa (suprabasal tumor region) 9 kPa (basement membrane tumor region)		
		Invasive squamous cell carcinoma (solid tumor)		25 kPa (suprabasal tumor region) 3 kPa (basement membrane tumor region)		
		Breast cancer (solid tumor)	Range: 150–300 nN	4 kPa		
Embryo	*Xenopus laevis*	Blastopore closure	300 nN to 2 μN	1.5- To 6-fold increase in stiffness		
		Leading edge mesoderm	20–80 nN			
		DMZ explants	1.2 μN			
	Newt	Gastrulation		23 Pa		
	Chicken	Primitive streak		Stiffness oscillations		
		Neurulation (neural folds)	50 nN			
	Zebrafish	Surface tension on the yolk at 50 % epiboly	66 pN/μm			
		Surface tension on the yolk at 90 % epiboly	110 pN/μm			
		Surface tension on the yolk at ~3.0 h post-fertilization		200–250 Pa (normal traction force)		
	Mouse	Blastocytes		1 kPa (normal traction force), 100 Pa (shear traction force)		
		E18.5 skin, dermis (*ex vivo* explant)		1 kPa		
		E18.5 skin, basal epidermis (*ex vivo* explant)		5 kPa		
		E18.5 skin, spinous and granular suprabasal layers (*ex vivo* explants)		11 kPa		
		Stratum corneum (*ex vivo* explant)		40 kPa		
	Drosophila	Gastrulating embryos (one cell)	2 pN			
		Gastrulating embryos (one cell apex)	0.5 ± 0.2 nN			
		Stomodeal primordium	60 ± 20 nN			
	Triturus alpestris	Neural folds	500 nN			
	Siredon mexicanum	Neural folds	900 nN			
			Range: 1 pN to 2 μN			

Regarding textural gradients, the elastic modulus (ratio of stress to deformation) of most normal tissues ranges from 0.5 to 15 kPa (see Table 1). In comparison, the fibrotic ECM can be 10 to 100 times more stiff.[33] It is also notable that the ECM stress of a healthy breast tissue is < 0.5 kPa, whereas that of a breast tumor tissue ranges from 5 to 20 kPa, as measured by atomic force microscopy.[34] Consistent observations demonstrated that an ECM stress of 20–25 kPa induces metastasis in oral squamous cell carcinoma[35] and epithelial ovarian cancer.[36] Values for metastasis induction in breast cancer are >5 kPa[37] (Table 2). Solid malignant tumors have greater stiffness in the invasive front than healthy tissues or even benign tumors.[38] This difference has been reported in breast,[34] pancreatic,[39] hepatic,[40] and prostate[41] cancers. Increased matrix stiffness shows a positive relationship with tumorigenesis and invasiveness through increased cell proliferation, cell motility, and invasion.[42,43,52,44–51] Thus, the stiffness of the tissue matrix serves as a marker of cancer risk and allows identifying tumors with a high risk of malignant transformation.[40]

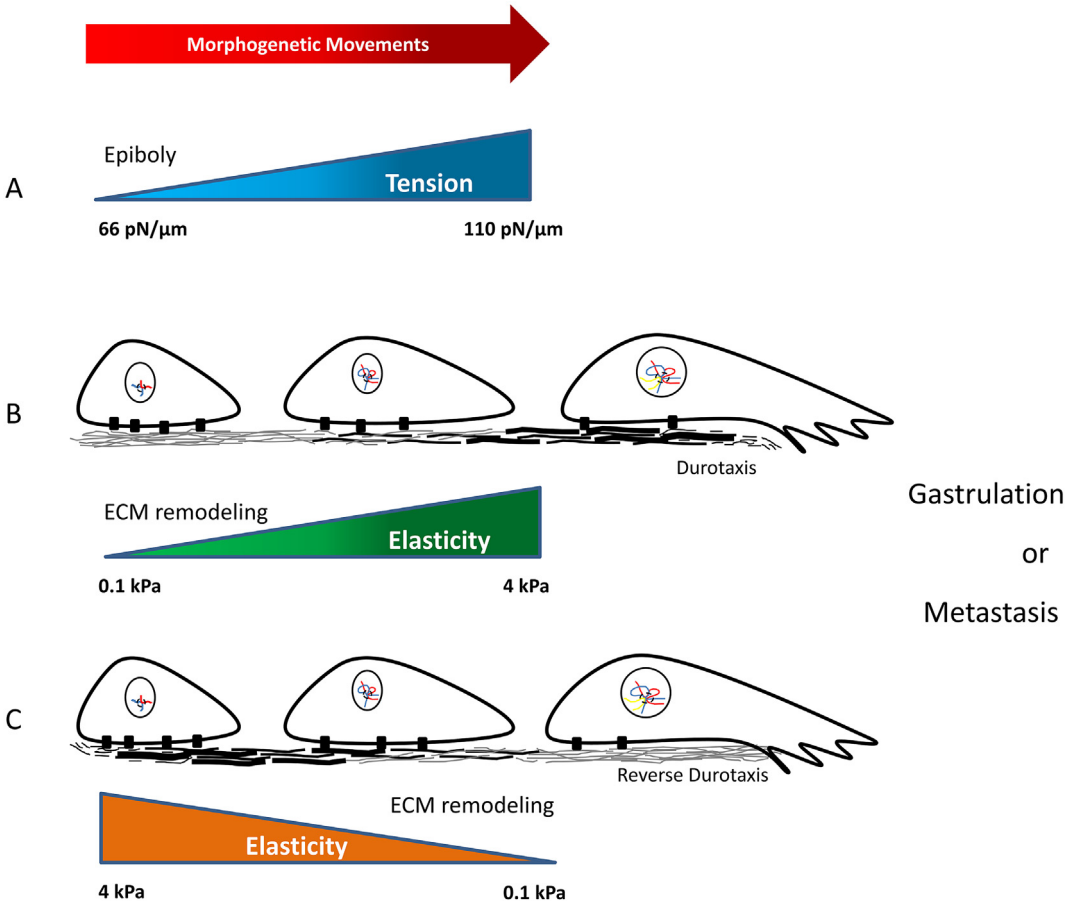

Fig. 2. Mechanobiology of embryogenesis and cancer. The red arrow shows the direction of embryogenesis and morphogenetic movements. **A.** During epiboly, there is an increase in surface tension, as reported in zebrafish embryos. **B.** In metastasis models, an increase in stiffness is observed, resulting in changes in morphology and migratory capacity similar to epithelial–mesenchymal transition (EMT). Stiffness gradients were shown to play an important role in the differentiation of mesenchymal stem cells and in the early development of mouse embryos (see Table 2 for information on types of cancer guided by durotaxis). **C.** Some types of cancer (see Table 2) are guided by reverse durotaxis.

The concept that cell movements are preferentially guided toward a stiffer substrate (durotaxis)[53] has been challenged by a number of observations of migratory movements toward soft substrates (reverse durotaxis) in cancer and embryo tissues.[31,54] Despite the existence of a hypothesis proposing that cell gears (integrins, actin filaments, and talin), along with excess force on a stiff substrate and frictional sliding, might explain symmetry breaking, cell polarization, and migration toward soft substrates,[55] this model remains insufficient. It seems more reasonable to consider an integrated proposal combining other mechanical cues, such as electrotaxis and the intense dynamic reorganization of the intracellular and intranuclear cytoskeleton in the production of forces.[56] This view is supported by the fact that actin filaments act as calcium-conducting bionanowires[57] that create electrical gradients. Calcium ions have an undeniable role in some types of cancers,[58–60] and persistent mechanical memory phenomena are also dependent on them.[61]

Tensile forces are significantly increased in human metastatic breast, prostate, and lung cancer cell lines compared to non-metastatic ones.[62] For example, the non-tumorigenic mammary epithelial cell line MCF10A produces tensile forces of 150 nN ($|F|$, calculated as the integral of the force over the entire cell area). On the other hand, highly metastatic cancer cells (MDAMB231) produce tensile forces of ~300 nN and generate traction stresses of 500–1200 Pa on the substrate (Table 2). Interestingly, increased matrix stiffness and density promote contractile forces through distinct mechanisms. Collagen density seems to enhance cell force generation by directly mediating cell spreading, whereas matrix stiffness appears to increase cell forces independently of cell spreading.

In an experiment comparing the tension in focal adhesions and viscoelastic properties of metastatic breast cancer cells (MDAMB231) and normal human breast cells (MCF10A), cancer cells showed higher tension in talin proteins and increased elasticity on stiff substrates[63] than normal breast cells. Increased tension in focal adhesions leads to increased actomyosin contractility, which further enhances the tension in focal adhesions.[64] Likewise, metastatic prostate cancer cells have been reported to be more contractile than healthy cells.[41]

In fact, increased stiffness and contractility are emerging as biomarkers of metastatic progression. Stiffer matrices reminiscent of the tumor microenvironment cause metastatic cells to contract more strongly, further promoting tumorigenic phenotypes[41] (Fig. 2). As will be presented below, oscillations in ECM stiffness (textural gradients), as well as variations in the production of tension and compression forces, are hallmarks of embryogenesis[32,65–67] (see Table 2 for comparisons between cancer and embryo cells). To perform gastrulation, the embryo responds to mechanical cues to achieve spatially oriented collective migration and induce cellular invasiveness for its own reorganization (a truly controlled metastasis), recording these forces in the form of mechanical memory.

Consistent with this idea of variations in ECM stiffness, textural gradients of ECM were observed *in vivo* during animal embryogenesis, much like what happens in cancer,[7,68–70] favoring migratory and invasive movements. In chicken development, the primitive streak is the site of cell ingression for mesoderm and endoderm formation. At Hamburger–Hamilton (HH) stage 5,[71] the textural network of the ECM adjacent to the primitive streak is smooth and thin. In a short period (about 3 h), from HH5 to HH6, the ECM texture shifts to relatively coarse/rough.[68]

This change takes place at a crucial moment of embryogenesis, that is, when EMT is occurring, and cells are migrating naturally and controllably to form the mesenchyme and endoderm. Therefore, the spatiotemporal dynamics of tissue stiffness *in vivo* seem to be decisive for embryogenesis.

The stiffness of embryonic tissues can change significantly within tens of minutes. In this short period, a stiffness gradient emerged in the developing brain of *Xenopus*, and the axons of retinal ganglion cells oriented themselves along this gradient.[66] Spatiotemporal quantification of the viscoelastic properties of a zebrafish embryo suggested that the posterior elongating region has lower stiffness and higher viscosity than the anterior region.[66] In another study, skin analysis of mouse embryos (*ex vivo*) allowed quantifying the stress produced in the suprabasal layer, shown to be approximately 11 kPa. In the same model, the stress on the suprabasal layer in premalignant basal cell carcinomas was shown to be 10 kPa, differing greatly from the stress in invasive squamous cell carcinomas, measured at 25 kPa[67] (see Table 2). These findings indicate that tumor-specific suprabasal stiffness gradients are formed as oncogenic lesions progress toward malignancy. Additionally, oscillations in tensile forces were detected in mouse blastocysts.[32]

Commensurate with these observations, *Xenopus laevis* embryos were shown to become stiffer during gastrulation, when collective migratory movements of convergent extension and cell intercalation take place. A 2- to 5-fold increase in stiffness was recorded during blastopore closure.[69] The blastopore is the region through which cells that will give rise to the endoderm and mesoderm invaginate. Rather than constituting a static group of cells, the blastopore lip is a dynamic annular mass composed of surface epithelia and deep mesenchymal cells that are collectively migrating.[72] Research on *Xenopus* suggested that force generation increases proportionally with increasing stiffness, and softer matrices produce lower apical stresses during contractions in the blastopore.[70]

Measurement studies of the forces required to produce sustained blastopore closure during gastrulation in *Xenopus* embryos yielded values ranging from 300 nN to 2 μN.[73,74] These forces, produced by an embryonic territory characterized by intense collective migration, are equivalent to the forces produced by the mammary metastatic cells MDAMB231 on a stiff surface (12 kPa)[62] (Table 2). Coherently, the structural stiffness of the blastopore increases 1.5 times during closure.[73] However, the forces generated by mesoendedermic cells migrating through the blastopore, specifically by the leading edge mesoderm that migrates prior to the axial mesoderm, were estimated at 20–80 nN.[75] These values are equivalent to the force exerted by metastatic lung adenocarcinoma cells (A549) on a stiff substrate (see Table 2).

Finally, studies measuring the forces exerted by the neural folds during neurulation can provide valuable information, as these embryonic structures perform EMT and give rise to neural crest cells—migratory cells that invade several embryonic tissues.[76] Classical force experiments using ferromagnetic dumbbells revealed neurulation forces in the range of 500–900 nN in two amphibian species.[77] Measurements taken by attaching elastic spring-like sensors directly to neural tubes undergoing closure in chicken embryos revealed forces of 50 nN.[78] Overall, these investigations demonstrate that oscillations in force production and tissue stiffness have an equivalent relevance in embryology and oncology. Now, this equivalence will be discussed in the context of embryonic stem cells and cancer stem cells (I recommend reviewing the challenges surrounding the concept of cancer stem cells, a debate that began more than two decades ago and persists to the present day[79]).

A soft matrix is known to promote the self-renewal of embryonic and cancer stem cells[80–83] (see Table 2). Murine embryonic stem cells retain their pluripotency when grown on a soft substrate (0.6 kPa) and lose their pluripotency and self-renewal ability in stiff culture environments. Stem cells grown on soft gels experience low tensile forces on the cytoskeleton, which contributes to preserving their pluripotency.[80]

Embryonic genes such as *Sox2*, *Oct4*, and *Nanog* (which are essential for normal embryonic development) are related to the self-renewal of cancer stem cells. *Sox2* expression in Hep-2 laryngeal cells increased when cultured in a 1 kPa substrate compared to a 8 kPa substrate; such expression was associated with a higher aggressiveness of cancer stem cells.[84] Likewise, osteosarcoma tumor cells grown on a 7 kPa substrate were less susceptible to doxorubicin than those grown on 20 kPa or 55 kPa substrates, and exhibited increased expression of Sox2, Oct4, and Nanog.[85] Sox2, Oct3/4, CD133, and c-kit were expressed in murine melanoma cells (B16F1) cultured on soft substrate.[82]

Consistent with oscillations in embryo stiffness, increased matrix stiffness is directly related to the characteristics of cancer stem cells presented by human hepatocellular carcinoma Huh7 and Hep3B cells. Such a property promotes self-renewal, proliferation, and migration in a stiff microenvironment. The number of cancer stem cells increases as the stiffness of the matrix increases.[86] Additionally, high matrix stiffness may promote nuclear translocation of TWIST1 (an embryonic developmental protein involved in dorsal/ventral polarity), inducing EMT in breast cancer and promoting tumor invasion and metastasis.[87]

These findings suggest that oscillations in matrix stiffness may have diverse implications for cells showing similar characteristics to cancer stem cells in various tissues, justifying the study of mechanical clues in embryogenesis and opening pathways for *in vivo* investigation of the physics of cancer. The purpose of studying the spatiotemporal dynamics of embryonic forces is to find new, advanced, and effective therapeutic approaches to eradicate cancer stem cells based on similarities arising from the neoplastic origin of the embryo.

Finally, from the point of view of my hypothesis, adult stem cells with embryonic memories occurring in an inappropriate context, for example, fluctuations in ECM stiffness, can trigger the induction of a metastatic process in humans. It remains to elucidate the foundations that support the formation of persistent memory in embryonic and cancer stem cells.

3. Considerations on the epigenetic foundations of long-term mechanical memory storage in embryos and cancer cells

The concept of epigenetics that best applies to embryology, cancer, and cancer stem cells is "the study of developmental processes in prokaryotes and eukaryotes that lead to persistent, self-maintaining changes in the states of organisms, their components, and their lineages".[88] One of the most fascinating current concepts is that of mechanical memory and its persistence (self-maintaining changes). Biophysical regulation of chromatin architecture produces stable remodeling and long-term changes in cell behavior instigated by mechanical signals.[33,61,89] Short-term mechanical memory depends on the contractility of actomyosin. Long-term increases in deformation that persistently affect chromatin condensation do not seem to depend on actin contractility, but rather on calcium ions.[61] Persistent and long-term memory could also be actin-dependent, as these microfilaments have gained reputation as bionanowires capable of conducting calcium waves.[57]

The concept of mechanical memory is central to embryology. The physical and mechanical experiences involved in the successful construction of the first embryo, when persistently embedded as mechanical memory in germ cells, could help reconstruct this process in subsequent generations. This mechanism gives rise to the concept of totipotency linked to persistent mechanical memory, as will be discussed later. The epigenetic mechanisms used to form and maintain mechanical memory are the main target of current scientific research.[61,90–92] Embryo cells store mechanical memory in part through the epigenome and chromatin architecture, that is, through biochemical modifications and the physical organization of the genome, all of which are sensitive to mechanical forces.[93–95] Genetic factors associated with the hypothesis of this article, such as the Hippo pathway, RUNX2, and other known oncogenes and tumor suppressors, are thoroughly described elsewhere.[1]

The participation of epigenetic mechanisms in the storage of the cell's mechanical memory is well known. There is a consensus that mechanical forces alter chromatin accessibility and transcriptional capacity. Chromatin accessibility has gained a significant role in the context of cancer, and Flavahan proposed a concept of restrictive and permissive chromatin

states.[96] Both states can influence cancer progression: a restrictive state can hinder the expression of tumor suppressors, and a permissive state can favor oncogenic changes. Therefore, mechanical factors that alter chromatin remodeling are capable of inducing tumorigenesis.[97] Is this alteration of chromatin remodeling a long-term and persistent process? Unfortunately, persistent epigenetic changes that potentially form mechanical memory have not yet been identified in cancer cells. But, can cancer cells form mechanical memory? Yes. This has been observed in response to the high stiffness of the ECM[98,99] and in *in vivo* models of cancer.[37,100]

Initially, it was hypothesized that long-term mechanical memory may be encoded in persistent epigenetic changes,[33] including histone methylation, histone acetylation (regulated by methylases, demethylases, histone acetyltransferases, and histone deacetylases), and methylation of DNA and non-coding RNAs.[90] Fortunately, this hypothesis was corroborated in non-cancerous cells.[61,89] Additionally, the non-coding RNA miRNA-21, which persistently maintains mechanical memory in mesenchymal stem cells, has been shown to be upregulated in several types of cancer and promote both tumor growth and metastasis in breast cancer.[90] This finding suggests that the hypothesis raised by Balestrini[33] is probable and plausible in a cancer context.

The strongest evidence for persistent epigenetic mechanisms in cancer lies precisely in embryology. Polycomb group proteins are epigenetic modifiers involved in the control of gene repression. They regulate developmental genes in various cell types and tissues, including embryonic and adult stem cells, and are essential for cell fate transitions in embryogenesis..[101] Polycomb group proteins have specific functions in embryogenesis, pluripotent stem cells, and the reprogramming of somatic cells to a pluripotent-like state.[102]

Normally, histone acetylation is related to gene activation and chromatin decondensation..[103] By contrast, trimethylation of lysine residue 27 in histone 3 (i.e., H3K27me3) is generally linked to gene repression.[104,105] H3K27me3 trimethylation occurs through the methyltransferase activity of polycomb repressive complex 2 (PRC2) and can increase local chromatin affinity for polycomb repressive complex 1 (PRC1).[106] The binding of PRC1 to H3K27me3 marks can lead to heterochromatin formation, loss of chromatin accessibility to the transcriptional machinery, and subsequent transcriptional repression due to chromatin compaction.[107,108]

Consistent with persistent memory, the application of a dose-dependent mechanical tension cycle in multipotent epidermal stem/progenitor cells and mesenchymal stem cells induced H3K27me3-dependent chromatin condensation and consequent transcriptional repression.[95,109] The increase in mechanical dose led to an increase in the magnitude and persistence of chromatin condensation in mesenchymal stem cells, indicating a dose-dependent nature of repression.[109] More information on this topic can be found in the thorough review of the subject performed by Dai and coworkers.[110] Therefore, embryonic stem cells—and, as evidence has indicated, cancer stem cells—have mechanisms for the formation and maintenance of long-term mechanical memory, which is essential for the emergence of animal phylogeny.

The actual beginning of animal phylogeny could only occur when all the necessary mechanical processes were in place within the first embryo. By coopting and organizing chromatin, the first zygote in history translated into the cell nucleus the physical impact of multiflagellate fusion and the intense reorganization of the actin cytoskeleton to which this cell was subjected. The same happened with cells that performed epiboly and cells that adhered to a basal lamina, receiving the physical impact of morphogenesis. Thus, within a short period of time in the life of the first embryo, a set of multipotent stem cells became able to receive and absorb the physical and mechanical impacts to which they were subjected during ontogeny. These stem cells were imbued with biomechanical history, stored in cell nuclei in the form of biomechanical memory, which would be used to reconstruct this process in the next generation (Fig. 1C).

Consistent with my proposal, basal animals were found to exhibit delayed segregation of the germline from a multipotent stem cell lineage,[111–113] coinciding with one of the most striking characteristics of cancer stem cells. This late separation is completely expected and necessary for the beginning of animal life. In the first embryo, multipotent stem cells first had to receive mechanical and physical stimuli from embryogenesis to trigger germline segregation. This situation evokes the philosophical question of what came first, the chicken or the egg? The answer is unequivocal and well consolidated: the egg came first, but with one caveat—it formed only after being fully impregnated by its surroundings and the inner physical trajectory of the first embryo.[1] This first embryonic journey is aptly described by the words of a Spanish poet, "Walker there is no path, you make the path by walking".[114] Therefore, the embryo modeled the genomic records of its construction during embryogenesis, creating a genuine mechanical memory[61,110,115] within multipotent stem cells. This principle is absolute for the first embryo, which established a topological map of Physics in the genetic material[116–119] (Fig. 1). Lending support to the conceptual framework of this article, *in vivo* models of mechanical memory have been explored in cancer research.[37,100]

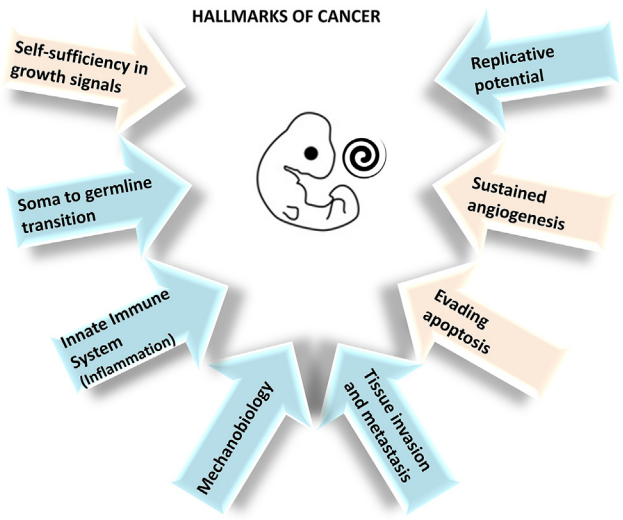

Fig. 3. The hallmarks of cancer within an embryological framework. The image shows a representative example of an animal embryo and does not imply that the framework is based on vertebrate embryology. The symbol at the center denotes the evolution of structural coherence acquired in the first embryo through biomechanical impacts. All hallmarks of cancer are necessary for embryo formation. The most ancestral hallmarks (from ctenophores) are shown in blue. Two new hallmarks are included: mechanobiology and soma-to-germline transition. Classic hallmarks, acquired much later during evolution, are indicated in red (e.g., angiogenesis, which does not occur in basal animals such as ctenophores and sponges). Red hallmarks were incorporated at different times throughout animal evolution.

This mechanical memory could be altered in time and space, creating hopeful monsters[120] reminiscent of a physical version of Stephen J. Gould's ideas.[121] This observation may hint at the mechanical underpinnings and rapid evolution resulting in the most wonderful diversity of forms seen throughout animal phylogeny. The biomechanical basis of evolution from ctenophores to sponges will be explored in a separate article.

Below, we will draw the parallels that lead to understanding cancer stem cells as a unifying principle between oncology and embryology.

4. Non-cancer and cancer stem cells are two sides of the same coin

The hallmarks of cancer have been extensively discussed and researched, including relevant aspects of the tumor microenvironment.[122] Nevertheless, certain crucial hallmarks have been overlooked—precisely those indicating that the disease is an evolutionary

and deeply embryological phenomenon. Cancer is not exclusive to humans; it occurs in all groups of animals. Furthermore, cancer exhibits reproductive features (soma-to-germline transition)[123] and an innate immune system created in the context of the first embryo[124] (Fig. 3).

Scientific evidence indicates that soma-to-germline transition is involved in tumorigenesis in metazoans, as this phenomenon contributes to the acquisition of neoplastic characteristics.[125,126] Several studies in *Drosophila melanogaster*,[127] mice,[128] and humans[129–131] showed that tumors ultimately enter a state closely resembling that of the germline. It is also known that germline genes drive oncogenesis in *D. melanogaster*[127] and are associated with clinically aggressive tumors in humans.[131] Additionally, activation of human orthologs of *D. melanogaster* germline genes triggers cancer.[127] These findings show the close link between cancer and animal evolution. Accordingly, it has been unequivocally proposed in the scientific literature that soma-to-germline transition is a universal hallmark of cancer in humans[129] (Fig. 3) and, apparently, in all metazoans.

An important question that remains to be fully answered is: Which germline genes are expressed in cancer? Mutations in the lethal(3)malignant brain tumor gene (*l(3)mbt*) induced tumor growth in the brain of *D. melanogaster* larvae. Inactivation of any germline gene, such as *nanos*, *vasa*, *piwi*, or *aubergine*, suppressed malignant tumor growth induced by *l(3)mbt* mutation, indicating that these genes play essential roles both in tumor development and suppression.[127] The genes *vasa*, *nanos*, and *piwi* were associated with spermatocyte differentiation and the onset of meiosis.[132] Thus, soma-to-germline transition could contribute to the acquisition of malignant features, such as rapid proliferation, lack of phenotype differentiation, and immortality.

Soma-to-germline transition in *Caenorhabditis elegans* is associated with vulval development, embryonic development, and morphogenesis.[133] The vulva of *C. elegans* is a hermaphrodite-specific ectodermal organ that develops post-embryonically. Its function is to connect the internal reproductive system to the external environment.[134] The vulva is necessary for mating (males inject sperm through the organ) and for embryo deposition after internal fertilization. Consistent with the hypothesis of a neoplastic process, vulval morphogenesis involves many of the same cellular activities underlying cancer, such as oriented cell division, cell–cell adhesion, cell migration, cell fusion, ECM remodeling, and cell invasion, among others.[134]

These associations demonstrate a conserved functional relationship in metazoan evolution between tumorigenesis and germline gene expression or reproductive organ morphogenesis.[133] Such a relationship makes sense in the context of my proposal of Neoplasia as an evolutionary engine. It is important to note that the genes *nanos*, *piwi*, *vasa*, and *aubergine* are not related to the germline of ctenophores. Knowing which genes are responsible for germline separation from the first embryo may have direct consequences in finding therapeutic targets when considering an ancestral mechanism of animal evolution.[135] An evolutionary look at cancer in the embryological context will allow reaching new targets and biomarkers with clinical potential.

Finally, it remains to answer the most important of questions: Why are genes specific to germ cells or reproductive organs so abundantly expressed in human cancer? Some hypotheses suggest the existence of a true "reproductive program" of the germline that is intrinsic to cancer development.[123] My hypothesis tries to show that the neoplastic process is intrinsic to embryogenesis, which would explain why multipotent cells like cancer stem cells reveal this reproductive aspect that is essential for the emergence of animal phylogeny.

The embryo is the only emergent property in which both the germline and incorporation of reproductive aspects are essential to ensure the success and repetition of the structural coherence of the animal in the next generation. If the embryo is accepted as a differentiated benign tumor,[136] stem cells can then be considered as the unifying principle of embryology and oncology. The success of the first embryo would be guaranteed by its establishment and separation from a set of multipotent cells, the germline. It would also create the organic structures necessary

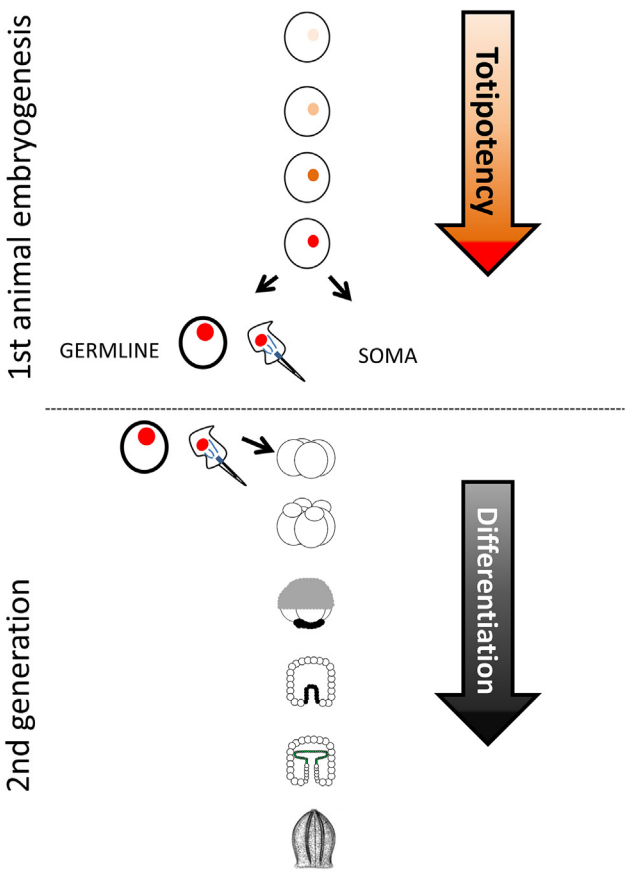

Fig. 4. Totipotency originated from mechanical impacts occurring during the first animal embryogenesis. As embryogenesis progresses, cells consolidate a form of mechanical memory that allows the process to be reproduced in the next generation. Multipotent cells, when differentiating into somatic and germline lineages, form germ cells that are totipotent (red nuclei in oocytes and sperm cells). In the figure, totipotency is represented by the intensity of the color red. In the subsequent generation, after fertilization, the zygote begins to reveal the mechanical process embedded in these cells. It should be noted that part of the revelation of this mechanical memory depends on the neoplastic force implicit in embryogenesis. Thus, in the second generation, the repetition of morphological events and the consolidation of the neoplastic functional module (NFM) take place. If the process is successful from an evolutionary point of view, the first definitive animal form is established and persists. Differentiation is another event that reveals itself in embryogenesis. The process is indicated by an arrow, whose color shifts from gray at the beginning of embryogenesis to intense black at the end. Changes in developmental pathways (co-option into the NFM or different external mechanical impacts) are possible and result in the appearance of diverse structures and shapes (hopeful monsters) throughout animal phylogeny. The figure implies that the first animal embryo was hermaphrodite.

for connecting the internal reproductive system with the external environment, allowing mating and embryo deposition after internal fertilization.

Therefore, the expression of genes associated with reproduction in human cancer reveals the embryonic side of the disease. Another way to reveal the embryonic face of cancer is by studying teratocarcinomas. Teratocarcinoma is a form of malignant germ cell tumor that occurs in both animals and humans. These tumors are very interesting for testing the hypothesis of neoplasia as a driving force of embryo patterning because germline cancers embody two distinct and opposing forces: the embryonic organizational force opposes the disruptive force of cancer (disease). G. Barry Pierce demonstrated the occurrence of embryonic organization in a small area of testicular teratocarcinoma. The mesenchyme and endoderm exhibited patterns that resembled the initial stages of embryogenesis and were called embryoid bodies.[137–139] Such

organization was also observed in a study by Winston Evans, who stated that embryoids "mimic closely the form of normal early human embryos".[140]

A conceptual basis for an embryological model of cancer has already been well established in Pierce's work; therefore, the dogmas that neoplastic forces are stable and irreversible haven been broken. According to Pierce, the control of cancer (teratocarcinoma) would occur through intrinsic mechanisms of the embryo (embryonic induction) involving cell differentiation.[137,141,142] Finally, evidence of the somatic origin of teratocarcinomas[143] reinforces the idea that embryonic somatic cells also have a mechanical record of the physical trajectory undertaken during embryogenesis. This concept is consistent with the evidence of a late separation of the germ line and somatic line in basal groups. Thus, some somatic cells would also contain, if not the same, at least equivalent mechanical information to that found in germ cells. In the terms discussed in this article, the similarities between cancer and embryology are rooted in the long evolutionary history of metazoans. This evolutionary perspective provides a foundation for understanding, preventing, and treating cancer.

For those of us who love evolution, cancer may be seen as a reflection of the cellular processes involved in our evolutionary origin. The neoplastic force at the heart of animal evolution managed to form an embryo and all the wonderful diversity of living animal forms after leading the physical environment to impregnate the nucleus of multipotent stem cells and ensuring the separation of somatic cells from germ cells (Fig. 4).

It is not known how long or how many attempts it took to form the first embryo; it is only known that the process has stabilized. This idea is concordant with the paleontological theory of punctuated equilibrium of Stephen Jay Gould and Niles Eldredge.[121,144] It is also in line with phylostratigraphic analyses showing that a significant number of protein domains involved in cancer emerged with the onset of multicellularity[145] and, consequently, the first embryo. It can also be predicted that, after the stabilization period, Neoplasia (the main core of evolution) was contained. In inappropriate contexts, whether in the embryo or the adult animal, this force becomes a disease (cancer), with occasional or recurrent events in all animal groups.[20,21]

5. Considerations about totipotency in cancer and non-cancer stem cells

First, I must highlight the fact that mechanical impacts during morphogenesis influence the formation of mechanical memory,[115] which was imprinted in the first embryo. The result of such impregnation can only be evaluated in the subsequent generation (second generation) (Fig. 4). That is, the success of the first embryogenesis can be assessed via physical records left in the genetic material of germ cells of the first embryo (I recommend an excellent review on germ cells in the evolutionary context[146]). These germ cells, derived from the first embryogenesis, were totipotent (see the expanded concept of totipotency in 147). Given that animal multicellularity was only possible by fertilization, the totipotency of a zygote stemming from mechanical events was only expressed in the first embryo. Was the zygote that formed the first embryo totipotent? From an animal point of view, no. The potency of the first zygote reflected cellular processes of unicellular Holozoa. Were the zygotes produced by fertilization of mechanically impregnated germ cells in the first embryo totipotent? Yes.

Scientific evidence has hinted at the possibility of drawing a physical topological map in genetic material,[118,119] suggesting that chromatin architecture is deeply interrelated with gene regulation.[148,149] Some clues about this physical map point to a highly organized and structured state[150] surprisingly conserved throughout evolution.[150,151] This organization occurs through topologically associating domains (TADs) and chromosomal loops found in germ cells and animal zygotes.[152,153] There is a natural tendency to think that totipotency is reached after fertilization.[153] However, totipotency only reveals itself after fertilization and the beginning of what we call the second generation of embryos (Fig. 4).

Another important clue to the impact of physics on embryogenesis is found in cohesins. These proteins mediate the formation of chromosomal loops and TADs of embryonic stem cells[154,155] and are sensitive to mechanical forces[94] (Table 1). Therefore, zygote organization and structure resulted from the first physical impact on the first embryo. PRC2, which interacts physically and functionally with G9a/GLP,[156] participates in a mechanosensory mechanism dependent on F-actin and the protein emerin[95].

One last clue of the physical map is found in the extensive remodeling of chromatin after fertilization. This process involves *de novo* trimethylation of histone H3 at lysine 9 (*de novo* H3K9me3) by the G9a/GLP complex. Labeling facilitates the subsequent establishment of a mature constitutive chromatin[157]. That is, *de novo* H3K9me3 ″bookmarks promoters for future compaction",[158] "creating a less constrained epigenetic environment for subsequent zygotic genome activation".[159] When heterochromatin is fully structured, H3K9me3 plays an important role in genome stability and maintenance of cell differentiation fidelity.[160] In my point of view, the ability of H3K9me3 to anticipate what comes next in embryonic development (mechanical memory) is only possible because it marks the physical map of the germline after fertilization.

Finally, in my hypothesis, multipotent cells have a three-dimensional (3D) chromatin structure that resembles gastrulation, morphogenesis, and cell differentiation. In this way, the structural complexity of the embryo is placed inside the nucleus. One of the representations of this 3D structure is the so-called "ground state",[153,157] also known as totipotency. This allows affirming, with a high degree of confidence, that the totipotency of the embryo is revealed through its physical construction (Fig. 4). It may also explain why non-cancer and cancer stem cells recapitulate embryogenesis and express germline genes. This behavior reveals the degree to which embryogenesis is contained within a cancer stem cell. A complete review of the consequences of morphogenesis on cell differentiation, in the conceptual framework of neoplastic processes, was recently published.[136]

Next, I will describe a hallmark that has been gaining strength in recent years. It shows that cancer, similar to the embryo, is a biomechanical phenomenon with an impact on nuclear architecture and gene expression (Fig. 3).

6. Embryo and cancer are two sides of the same coin: physical and mechanical foundations

There is evidence of the mechanical foundations of the neoplastic process. Subjecting epithelia to mechanical stress (of sufficient strength and persistence) produces metastasis (Table 2). This is also valid for morphogenesis, whereby gastrulation can be induced by strictly biophysical and mechanical phenomena[161,162] (Table 2). I specifically chose two crucial embryological events, epiboly and ECM remodeling during EMT (gastrulation), to exemplify the biomechanical impact on embryo emergence (Fig. 2). I will provide a counterpoint to evaluate and discuss the role of biomechanics in cancer.[37,163]

6.1. *Epiboly*

In embryonic epithelia undergoing marked proliferation in the presence of little to no ECM, such as those initiating epiboly,[164] actomyosin contraction results in the transmission of mechanical tension and stress over long distances via adhesion proteins[165] (Fig. 2A and Table 2). The orientation of cell divisions produced by mechanical tension was shown to mediate epithelial delamination during epiboly in *Danio rerio*, enabling the release of anisotropic tension as the epithelium expands.[9,166] A simple and unifying principle governs collective migration in non-embryonic monolayer cultures of endothelial and

epithelial cells: motion occurs along the orientation of minimal intercellular shear stress.[167]

For epiboly to occur, it is necessary to establish an integrated cytoskeleton network connected by E-cadherins with a mechanoreceptor function[168] and multicellular actomyosin cables,[169,170] forming a continuous and integrated tension network in the animal embryo. This architecture is what enables self-organization.[171]

Research integrating physics and embryogenesis has provided evidence supporting that the actomyosin cytoskeleton can act as a regulator of cell behavior and mechanotransduction through the generation of internal contractile forces.[172] Participation of the actomyosin cytoskeleton is crucial in multiple stages of embryogenesis, including cell division, growth, morphogenesis, and organogenesis[173,174] (Fig. 1C). Epiboly and other tissue-scale morphogenetic movements are governed by the dynamic remodeling of cell–cell adhesion at cellular interfaces.[175] Accordingly, the expansion of an epithelial monolayer is being increasingly understood as a mechanical phenomenon[176] entailing force transmission through adhesion complexes[177] (Fig. 2B and C). That is, biomechanic processes such as tissue geometry, cell division, and mechanical force interact to produce morphogenesis.[178]

Epiboly is essentially a process of epithelial expansion. In an expanding epithelium, each cell exerts forces on the underlying substrate.[179] Physical forces control movement direction and coordination,[180] generating mechanical waves.[181] Fascinating experiments have shown that the epithelium creates long-range stress gradients when transmitting forces through intercellular junctions,[182] akin to how morphogens operate.[173] Morphogens, one of the most important foundations of modern embryology, have always been approached from a purely chemical perspective.[183,184] Only recently have studies started integrating embryonic mechanics with pattern formation.[185]

The conceptual framework of this hypothesis supporting Neoplasia as an evolutionary engine places physical and mechanical properties as the cornerstones of cancer evolution.[186,187] Tumor progression is driven by expansion of the tumor mass and the increased contractility of tumor cells,[188] as seen in the first stages of embryonic development. A study using biophysical models of 3D collective cell migration concluded that mechanical waves are a common characteristic of cells that migrate together.[189] For instance, collective migration of a human carcinoma cell line (HCT116) produces a large-scale viscoelastic force influencing cell rearrangement and inducing the generation of mechanical waves[189] (Table 2). Thus, in line with the model proposed herein, mechanical waves would arise from long-term cellular rearrangement driven by viscoelastic and surface tension forces. Viscoelastic forces are resistive forces that appear opposite to the direction of cell migration.[181] If we consider the embryo as a distinct type of benign tumor, such forces could play a decisive role in establishing embryo polarity, representing a reinterpretation of morphogens from a physicochemical perspective.

An in-depth investigation shed light on the importance of tension networks to the formation of the first embryo by showing that mechanical tension regulates the Hippo pathway in *Drosophila*.[190] It follows from this finding that a mechanotransduction system comprising Hippo could be involved in cell proliferation, morphogenesis[190,] and mechanical memory.[191] There is also evidence of regulation and interdependence between adhesive phenomena and the cell cycle, with participation of components of the Hippo pathway.[192] This is truly a revolution in embryology. It marks the moment when cells learned to grow and migrate together, a milestone in animal phylogeny. The Hippo pathway emerges as a central mechanism through which cells take control of their behavior based on their shape and spatial location..[193] This ability is crucial for achieving embryo multicellularity and, notably, leads us to speculate that epiboly is a biomechanical movement, underscoring the significance of physics in embryogenesis and cancer.

The proposal of a neoplastic process at the heart of animal evolution carries implications for the embryological process and the migratory movements of cells in cancerous lesions. During epiboly, ectodermal epithelial cells perform a type of collective migration whose precedents lie in evolutionary history.[194] Accordingly, research has identified several modes of cancer cell migration, such as individual amoeboid, collective amoeboid, filopodial, and mesenchymal movements.[195–198] The origins of the collective migratory movements of cancer cells can be traced to the beginning of animal life. From this perspective emerged the proposal that epithelial and mesenchymal cancers recapitulate embryonic development.[12,13,199,200] In my viewpoint, cancers recapitulate their own origin as an evolutionary engine.

6.2. Gastrulation: ECM remodeling

The ECM plays essential roles in many processes during embryonic development, including morphogenesis, cell differentiation, migration, proliferation, and apoptosis.[201,202] In fact, ECM degradation or remodeling are key processes influencing tissue structure and cell function and behavior.[202] The main consensus concerning gastrulation is that it is a process governed by mechanical rules (Fig. 2B and C and Table 2).

Cellular mechanotransduction systems were found to trigger gastrulation in *D. melanogaster*.[161] In this animal, morphogenesis seems to be triggered by coordinated changes in cell shape mediated by integrins and driven by actomyosin contractions in the embryonic mesoderm. The process can occur in a Fog-dependent[203] or -independent[204] manner. Therefore, the endoderm would arise from a mechanically driven cycle of cell deformation, independent of gastrulation genes such as *twist* and *snail*. These genes have always been regarded as morphogenetic control genes.[205] Such a mechanism of gene-independent cellular deformation is compatible with pulsatile actomyosin networks found across numerous animal species.[206] In *D. melanogaster* and *C. elegans*, Ras homolog family member A (RhoA) and myosin II (MyoII) were shown to participate in gene-independent cellular deformation processes.[203]

Since the origin of metazoans, mechanotransduction, as a physical mechanism, seems to have a relevant role in morphogenesis. Cnidarians are of crucial importance for understanding the evolutionary transition from diploblasts to triploblasts, being representatives of basal groups. The invagination process in *Nematostella vectensis* seems to reflect a highly evolutionarily conserved mechanism, with expression of the gene *brachyury* around the blastopore,[207] whose regulation is dependent on β-catenin signaling.[208,209] In agreement with a biomechanical model of invagination, the blockage of MyoII-dependent gastrulation led to *brachyury* downregulation. However, gene expression could be rescued by applying external mechanical stress.[210] Recovery of *brachyury* expression by an external deformation force was found to be β-catenin-dependent.[210] Similarly, a study with triploblastic embryonic models demonstrated that mechanical deformation or application of a magnetic field, to mimic epiboly, induced β-catenin nuclear translocation.[211] Mechanical forces are also responsible for the expression of *notail* (*brachyury* homolog) in *D. rerio* and *twist* (mesodermal marker) in *D. melanogaster*.[211] Overall, these studies suggest that mechanotransduction processes involved in invagination are highly conserved in metazoans.

Therefore, physical forces would participate in embryonic events that result in cellular rearrangements and are dependent on ECM remodeling. Studies on *N. vectensis* revealed a well-consolidated ECM in the blastula[212] and an incomplete form of EMT.[213] These findings suggest that ECM remodeling phenomena occur in the background of mechanotransduction processes. Expression of the *brachyury* homolog was observed in Ctenophora, in ectodermal cells surrounding the blastopore.[214] Unfortunately, there are still no physical studies that associate its expression with mechanotransduction or ECM remodeling mechanisms. Furthermore, the role of MMPs in β-catenin nuclear translocation via mechanotransduction has not been investigated.[210,211] Nevertheless, there are numerous scientific articles relating ECM remodeling to mechanotransduction phenomena.[215] Thus, external biomechanical stimuli translate into biochemical signals that initiate cellular processes such as growth, proliferation, cell differentiation[216,] and embryonic morphogenesis.[217]

My hypothesis proposes that cancer and embryo were established together during evolution, and I can predict that *brachyury* expression is linked to cancer events. In cancer biology, *brachyury* has been associated with EMT, resulting in a more invasive tumor phenotype.[218] The idea that *brachyury* is the driver of EMT is well-established[219] for various types of carcinoma.[220] In fact, the protein has been explored as a target antigen in tumor vaccines.[221] *brachyury* expression is often associated with more aggressive forms of cancer and poor prognosis. Consistent with its embryonic location in the notochord,[222,223] *brachyury* has been suggested to be crucial for chordoma development and spread.[224] In my view, *brachyury* is part of a very ancient framework involved in the formation of the first embryo. Its location in the blastopore of Ctenophora[225] and role in the mechanotransduction system of Cnidaria[210] are factors that determine its early link with cancer.

As expected, currently, there seems to be a consensus that mechanical stress is associated with morphogenesis and cancer.[163] Organogenesis is subject to a multitude of tensile forces that shape morphology and differentiation.[226] Metastasis is also associated with dramatic changes in tension, which include elevated compressive forces, mechanoreciprocity, and increased ECM stiffness (Fig. 2B and C).[52] The chronic increase of these tension forces influences tumor growth, tissue morphogenesis, and invasion. In this context, the impact of mechanical force is widely known. Studies have evaluated the effects of its extent or persistence on mammary gland morphogenesis.[37] Other interesting articles showed that increased ECM stiffness (caused by collagen crosslinking) induced invasion of premalignant mammary epithelium[87,227,] as well as EMT in oral squamous cell carcinoma.[35]

Therefore, the link between EMT, cancer,[228] and embryology,[229,230] as well as their mechanical foundations, are indisputable. The supposed contradictions of classical EMT as a universal resource in tumor invasion and metastasis, which include incomplete EMT, reversion to epithelial phenotype, and collective migration, may be elucidated in the field of embryology. Incomplete EMT occurs in embryonic development of *N. vectensis*,[213] reversion to an epithelial phenotype is observed in MET for the formation of various embryonic structures,[14,231,232] and, finally, collective migration finds support in embryonic morphogenetic movements.[233]

To conclude my reflections on ECM, it is important to consider the amoeboid traits of unicellular holozoans.[4] It is not surprising that ECM remodeling allows revealing amoeboid traits in an embryonic context, given the phylogenetic origin of the first embryo. The three main cell types that have amoeboid movements are primordial germ cells (which receive the neoplastic module),[234,235] immune system cells,[236] and stem cells.[237] In cancer research, it is considered that amoeboid movements are not a means of migration but rather a cellular state.[238,239] Currently, mesenchymal–amoeboid,[240] epithelial–amoeboid,[241] and epithelial–mesenchymal–amoeboid transitions[242] are recognized in some cancers. All these transitions are consistent with my hypothesis about the evolutionary origin of cancer. Epithelial–mesenchymal–amoeboid transitions bring to mind embryo cells that carry[243–245] and modify[235] the ECM while migrating.

Finally, in this article, I intentionally referred to cancer stem cells as a unifying biomechanical principle. The aim was to underscore the importance of Neoplasia in embryo construction and highlight how neoplastic processes are closely intertwined with embryo formation and, consequently, the origin of animal phylogeny. I hope it has been made clear that normal stem cells are also a unifying principle, representing both sides of the same coin. The fine line that separates the two normal physiological processes for tissue construction/reconstruction (or even embryo formation by fertilization) and the disease cancer is the time and space at which developmental processes are initiated (cancer occurs in inappropriate contexts). Thus, we may see adult cells undergoing malignant transformation/metastasis, recapitulating embryonic history and activating germline genes that are coherent only within the biomechanical construction of an embryo.

7. Concluding remarks and perspectives

The main final reflection of this article is that cancer reveals our evolutionary and biomechanical history. Therefore, I speculate that the cure for cancer lies in the great developmental transitions and physical processes that support the diversity of metazoan body shapes. Inevitably, it is necessary to consider which contexts activate or deactivate cancer. The experiments of G. Barry Pierce are pioneers in the control and differentiation of teratocarcinomas in the embryonic context.[138] Therefore, physics and embryogenesis are perfectly imbricated around cancer. In line with this idea, I propose that embryonic differentiation controls the cancer side of the embryo. Thus, the animal embryo may be seen as a differentiated benign tumor.

I propose that a mechanical and evolutionary approach to embryology and cancer could transform modern medical practices. If physicists and biophysicists integrate embryology and cancer into their frameworks, we might shift focus from looking for a cure for breast cancer in *BRCA1/2*[246] to exploring diagnostic and preventive strategies based on textural gradients (and their temporal dynamics), mechanical stress, and remodeling associated with force persistence. Thus, the scientific approach would be adapted to changes in women's menstrual cycle. The growth and shrinkage of breasts during the menstrual cycle involve physical phenomena. I envision an immediate improvement in the methodological strategies for early tumor identification. Currently, it is possible to observe textural gradients in *in vivo* embryonic models[8] and measure the force and tension of epithelia. Therefore, physics may play a pivotal role in the creation of new therapeutic strategies.[247–250] By recognizing the embryonic and physical origins of cancer, we may uncover paths to a true cure through insights from animal evolution and major morphogenetic transitions. Although we still have little knowledge of its cure[251,] cancer is known to be deeply rooted in the structural foundations of animal development.

In the immediate and inevitable future, I believe physicists will appropriate embryology. In my humble opinion, physicists distanced themselves from embryology because of the influence of genes on the structural determination of the embryo. A major audacity of biological sciences was that genes were deemed the main factor influencing morphogenesis. The modeling of animal forms, structural similarities, and kinship has always had an exclusively genetic background. The current paradigm showed how physics can model the nucleus of a cell and influence gene expression and morphogenetic processes. Thus, genes would be only a small part of a large and complex biomechanical cellular process responsible for shaping living forms. Today we know that physical forces can activate morphogenetic processes in embryos with gene mutations said to be morphogenetic. This leads us to exclude cancer and embryology as genetically determined phenomena and rethink them (cancer and embryo) as a tissue organization process[252] with physical and epigenetic influence, being an integral part of a neoplastic process.

Therefore, it is time for a paradigm shift in science and a revolution toward a multidisciplinary approach to embryology. By studying the physics of development, we will be intrinsically studying the disease cancer, a disease with no cure but that, as we now come to understand, is an inherent part of our animal organization.

Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of competing interest

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