Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Sequential development of embryoblast like memory entities in human malignant tumors, an evidence of cancer cell metamorphosis retrodifferentiation.

Jairo Diaz (jaditod@hotmail.com)
Universidad Cooperativa de Colombia Facultad de Medicina https://orcid.org/0000-0002-8972-6769
Luis A Diaz
Universidad Cooperativa de Colombia Facultad de Medicina
Mairicio Murillo
Universidad Cooperativa de Colombia: Universidad Cooperativa de Colombia
Laura Poveda
Universidad Cooperativa de Colombia Facultad de Medicina
Katherine Mora
Universidad Cooperativa de Colombia Facultad de Medicina
Oscar F Suescun
Universidad Cooperativa de Colombia Facultad de Medicina
Monica Cardenas
Universidad Cooperativa de Colombia Facultad de Medicina
Laura Castro
Universidad Cooperativa de Colombia Facultad de Medicina
Liliana Sanchez
Universidad Cooperativa de Colombia Facultad de Medicina

Research Article

Keywords: Embryonic Genotype-phenotype, Individual Cellular Memory, Squamous Tumor Cells, Human Papilloma Virus, Somatic Injured Cells

Posted Date: February 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-192698/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Sequential development of embryoblast like memory entities in human malignant tumors , an evidence of cancer cell metamorphosis retrodifferentiation.

Jairo A Diaz [1,2,3,4] ; Liliana Sánchez [1] ; Luis A Diaz [1,2] ; Mauricio F Murillo [2] ; Laura Poveda [1] ; Katherine Mora [1]; Oscar F Suescun[1] ; Monica Cardenas [1] ;Laura Castro [3]…….

,

1. Faculty of Medicine, University Cooperative of Colombia, Villavicencio, Meta, Colombia

2. Laboratory of Pathology, Hospital Departmental of Villavicencio, Meta, Colombia

3. Hospital Regional de Granada, Meta Colombia

4. Laboratory of Pathology, Liga Colombiana Contra el Cáncer, Villavicencio, Meta, Colombia

*Corresponding author. E-mail: jaditod@hotmail.com

ABSTRACT

Every cancer cell can partially or completely return to an embryonic genotype-phenotype: We capture the cycle of the activation of an individual cellular memory, which allowed a group of squamous tumor cells with mutations caused by the Human Papilloma Virus to return collectively to an embryoblast- like entities . Somatic injured cells have the plasticity to transform their morphology into an embryonic phenotype by expression of dormant genes when they enter a state of cellular emergency

The hallmark of these entities is that its structure can exist in two visible chiral conformations and therefore behaves at distance molecular communication which results in clusters of malignant cells aligned in progressive order sequences, cancer cell metamorphosis retrodifferentiation recapitulate early stages of the embryogenesis with high immunopositivity expression for neuron specific enolase . Our findings document how malignant tissues reactivated ancestral storage memory and elaborate inside tumor glands crystalline proteins (Tc) biomimicry blastocyst- embryoblast fluid-filled cavity. Under physical cellular stress it is possible replicate these entities from the epithelium of minor salivary glands in humans determining that dormant genes expression can be induced by artificial stimulation. These observations confirm the importance of the foetal characteristics of cancer as a source of useful information that can contribute to better understanding of the biology of cancer at molecular, cellular and micro-

environmental levels , to develop new target therapeutic alternatives not only in cancer but also in treatment of autoimmune, viral diseases, in regenerative medicine and rejuvenation.

Introduction

The morphological patterns of malignancy have traditionally been exclusively based on the change in size and shape of cells or nuclei, abnormal mitosis and pleomorphic nuclei, hyperchromatic coarse clumped chromatin, a change in the nucleus/cytoplasm ratio, loss of polarity and disordered growth. We propose that this approach to cancer is incomplete.

In 1908, a pathologist at the University of Manchester, Charles Powell White, noticed that there was something more than hyperchromatism and pleomorphism in the tumor tissues. White [1] observed the presence of crystals in malignant tumors based upon the premise that alcohols dilute the crystals.

The author relates these crystals in some way to the proliferative activity of the tumor, identifying them both in sarcomatous lesions and carcinomas. The crystals are made up of cholestyramine, and fatty acids seem to be associated with cell proliferation rather than with cell degeneration. In 1963, George Rose from the Biology Department of the University of Texas identified unusually large extracellular crystals and particles produced by **embryonic** chick cells in special tissue culture environments, including helical, tubular, ribbon-like, triangular, hexagonal, rhomboidal and filamentous forms [2]. The origin of these forms was detailed biochemically, but their usefulness in the culture environments in which they were found remained obscure.

In 2007, in a preliminary study, we described and documented the self-assembly of geometric triangular chiral hexagon crystal complexes (GTCHCs) in human pathologic tissues at macroscopic and microscopic levels, particularly in cancer tissues [3,4]. The genesis of these complexes occurs through intercellular cancer collisions that lead to the degradation of membrane ejected actin filaments in the form of rotation–domain interactions – that is, pairs of filaments with left- and right-hand sub-patterns of spin spirals [5]. Recent observations confirm the previous findings on GTCHCs

identified in cancer tissues 10 years ago: interfacial geometry dictates cancer cell tumorigenicity [6], and matrix geometry determines the optimal cancer cell migration strategy and modulates responses to interventions. Whereas tumor cells exploit geometry for metastasis [7], the geometry helps confined cells to acquire a stem cell phenotype [8]. Today we postulate in accordance with our findings that this geometry of spirals and triangular patterns that we call triplet crystals (Tc) represents the crystalloid mold proteins on which the spatial order that gives rise to what we call embryoblast memory entities in malignant tumors is built.

Tumorigenesis resembles the self-organizing process of early embryo development. With the recent profound advances in the field of developmental biology, it has become apparent that the early development of embryos shares many similarities with cancer development in terms of both biological behaviors and similarities in the cell invasive epigenetic regulation of gene expression and protein profiling. Thus, it is evident that tumorigenesis mimics a self-organizing process of early embryo development [9–15]. The aim of this research is to demonstrate the intimate connection that cancer has with embryogenesis. **Cancer recapitulate early stage of embriogenesis**

Material and methods

We collected and re-examined all of our materials, in which we identified recurrent patterns of triangular and spiral chiral crystals (Tc) as geometric attractors, in cancer tissues. In the past 5 years, corresponding to more than 1077 microscopic/macroscopic specimens, including carcinomas, adenocarcinomas and sarcomas.

It is important to mention that the images documented in this work belong to living patients, with a natural history of cancer, who have not previously undergone chemotherapy or radiotherapy. The size of the giant masses documented show that they developed in approximately 9 years, with silent clinical growth. When these large masses were resected, none of these patients had developed metastases and it was for this specific reason that they were given the option of surgery as their condition allowed it.

Neuron-specific enolase – immunostaining

This isoenzyme, a homodimer, is found in mature neurons and cells of neuronal origin. Detection of NSE with antibodies can be used to identify neuronal cells and cells with neuroendocrine differentiation

Sixty formalin-fixed and paraffin-embedded tissue sections with the most representative hot spot of Tc identified in malignant tumors were analyzed using neuron-specific enolase . We performed immunohistochemistry using the standard protocol method with paraffin sections. The scoring was done as follows: Ni (no immunostaining); low (10% or less immunopositivity); or high (>10% immunoreactive cells).

Statistics analysis

The index of **Tc** geometric complex assembly in cancer tissues was determined, as well as neuron-specific enolase antibody immunostaining positivity index in correlation with Tc expression areas. Chi-squares for proportions were estimated using EPI-INFO software (v 6.04; Center for Disease Control and Prevention, Atlanta, GA, USA).

This study was approved by the ethics subcommittee of the University Cooperative of Colombia, Villavicencio, Colombia, and followed the guidelines of the Ministry of Health (No. 8430 of 1993) and the principles established by the Declaration of Helsinki. All patients signed an informed consent form for the use of their biological materials for diagnostic and research purposes.

RESULTS

From 1077 malignant tumors, **Tc** geometric complexes were identified in 1050 cases. These findings show identification of highly ordered geometric structures in more than 97.5% of the analyzed malignant tumor tissues ($P = 0.00001$; Table 1). Benign tumors and inflammatory entities do not evidence these structures. Tc represents the geometric triangular - spiral cleavage precursor in the formation of embryoblast entities.

Table 1

Identification of Tc in cancer tissues

Tumours		
Tc +	**Tc–**	**Final**
1050	**27**	**1077**
97.5%	2.5%	100%

Photomicrography evidence

We were able to capture a unique and perhaps unrepeatable image: the evolutionary cycle of structures with embryoblast- like phenotype generated from squamous epithelial cells injured by Human Papilloma Virus in a cervical cytology sample with cancer in situ. The cycle consists of 12 stages that show step by step how these structures are gestated.

As can be seen in the images, these entities are gestated from fractal crystalloid protein memory modules that have an **embryoblast like phenotype,** where clusters of malignant cells aligned in progressive order sequences with architectural metamorphosis from triangular - spiral cleavage microscopic -macroscopic structures, is activated when the cell suffers irreversible damage from specific mutations, as in this case through the action of the Human Papilloma Virus (Fig 1).

We identified three memory modules in this metamorphosis retrodiferentiation of these entities:

a) **Protein Crystalloid memory module**: Stages 1 to 6 (Fig 1).

We can observe the intelligent sequence of a chain of events. Protein Crystalloid entities measuring 4 to 9 um appear separate, aligned and functionally interconnected. In stage 1 we can observe a polar entity made up of 2 molecular crystals proteins of triangular and spiral shapes that appear in a chiral position. We had previously described this event as GTCHC complexes [3] With this evidence, we can now state that these complexes initiate the process and originate from molecular liquids generated by the secretion of glandular tumor epithelia. These liquids inside the tumor glands generate movements for and against the clock, creating real molecular whirlwinds from which the spirals and triangles are formed, and when they solidify, they represent the crystalloid proteins of this process, which is in essence an **eminently physical phenomenon**. We wish to draw attention to the images documented below that show how malignant tumor glands adopt an emerging **embryoblast** – **blastocyst** like function. Remember that the blastocyst is an embryonic structure

that forms during the early stages of development in which the morula develops as a fluid-filled cavity, transforming itself into a blastocyst or embryoblast.

In stages 2 to 5 we can see fractal copies of these protein crystalloid entities that have spontaneously replicated.

In stage 6, the entities gather all the information in a single structure and perforations can be seen on its surface. This entity full of holes on its surface and which we call Triplet Crystal (Tc) is constituted by a triplet of spirals and triangles perfectly and beautifully assembled spatially, which behaves as a mold-vector of biological information.

b) Cellular memory module

In stages 7 to 10 we can see the **biological phase**, which can be identified as the Tc pattern of stage 6 It behaves as a vector of biological information and transfers information to the nearby injured squamous cells, generating a change in these cells' normal polygonal cellular phenotype, sequentially acquiring the same pattern of the triangular phenotype of the **Tc.**

In stages 11 and 12 we can see the complete transfer of information from **Tc** to squamous cells, generating an exact copy of the Tc phenotype.

We can see how the transformed squamous cells progressively become more hyperchromatic as they reach stage 12, where an embryioblast like entity is clearly shown, completing the metamorphosis experienced by the squamous cells, probably regulated by the reactivation of genes and proteins that come from normal embryogenesis.

This evolutionary cycle shows other surprising details that speak for themselves: In the transition phase between stage 10 and 11, four pairs of triangular molecular satellite crystals can be seen near the squamous cells that are transforming their phenotype. These are once again perfectly visible in a chiral position (highlighted in a purple circle).

If we join the individual protein crystalloid memory modules with the spatially separated cellular memory modules, from stages 1 to 12, we obtain the spatial image of a perfect collective memory that has the phenotype of each of the individual memory entities. It can be observed how ""Every cellular collective" is identical to each of its individual cellular parts and each individual cellular memory has the phenotype of a collective memory encoded.

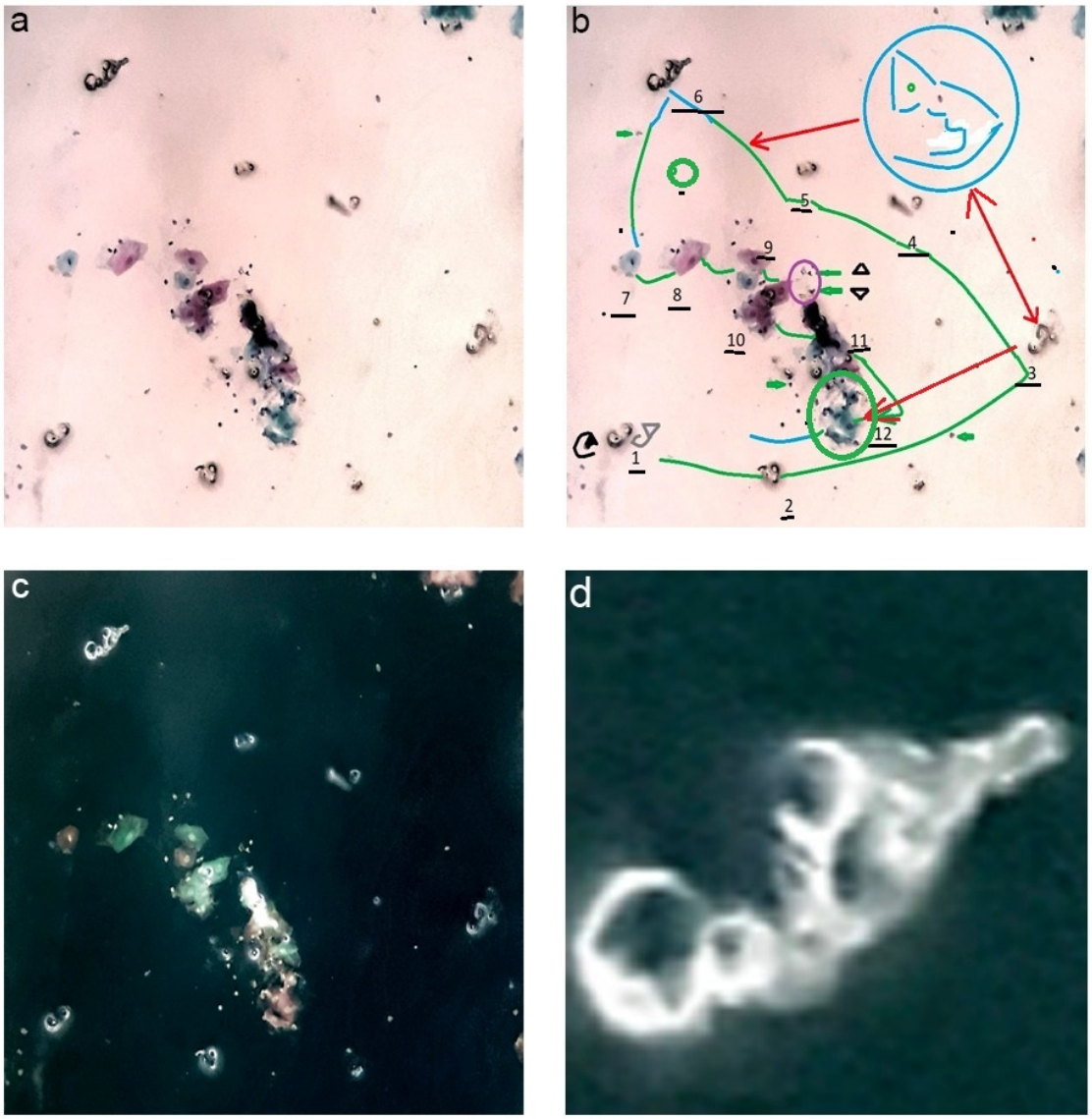


FIGURE 1

Clusters of malignant cells aligned in progressive order sequences with cell metamorphosis retrodifferentiation

With the unique patterns identified in this evolutionary cycle, we generated a prototype algorithm that allowed us to perfectly trace these entities in other tumor scenarios, and this is how we were able to identify them in carcinomas, adenocarcinomas and sarcomas. We had the opportunity to document these patterns in other scenarios under similar conditions.

Figure 2 shows in detail the triplet of modularly integrated components that form the **Tc** entity. We can observe how this entity emerges from the secretory activity of the tumor gland in the lumen of an endometrial adenocarcinoma simulating a **blastocyst-embryoblast.** (panels e1-e2). Tc represents the geometric triangular - spiral cleavage precursor in the formation of embryoblast entities

The architectural union of 3 spirals and 3 triangles organized spatially in absolute perfection forms what we call Triplet Crystal (Tc). We can observe how the tumor epithelial cells around them, indicated with a red circle, have acquired the Tc **phenotype** (Figure 2 panel m**).** These images clearly express, as never before, how the geometrical entity that orders Tc can somehow physically regulate the micro-macro cellular environment where these entities are gestated and self-assembled**.**

The Tc images show how this entity is an interface structure.

In panel h, A shows the **cellular biological** phase of the entity, given by its round phenotype, while B shows protein crystals and a geometric triangular-spiral pattern constituting the physical phase of the entity. At present, there is no evidence of a structure produced naturally where this structural conjunction between physics and biology can be so clearly observed, which makes this structure a mold to be copied and used in bioengineering as an entity that generates order and unique biological organization.

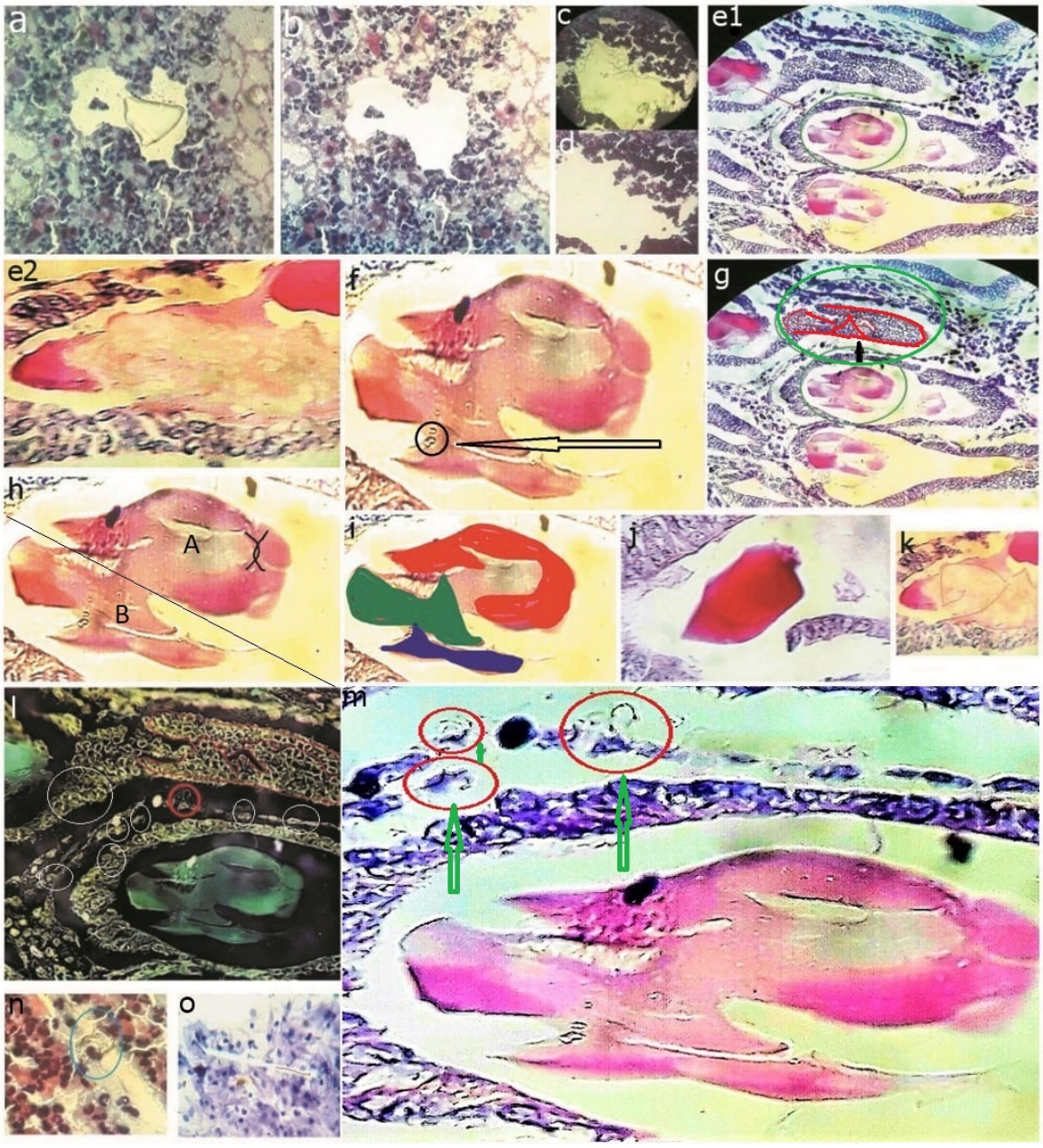
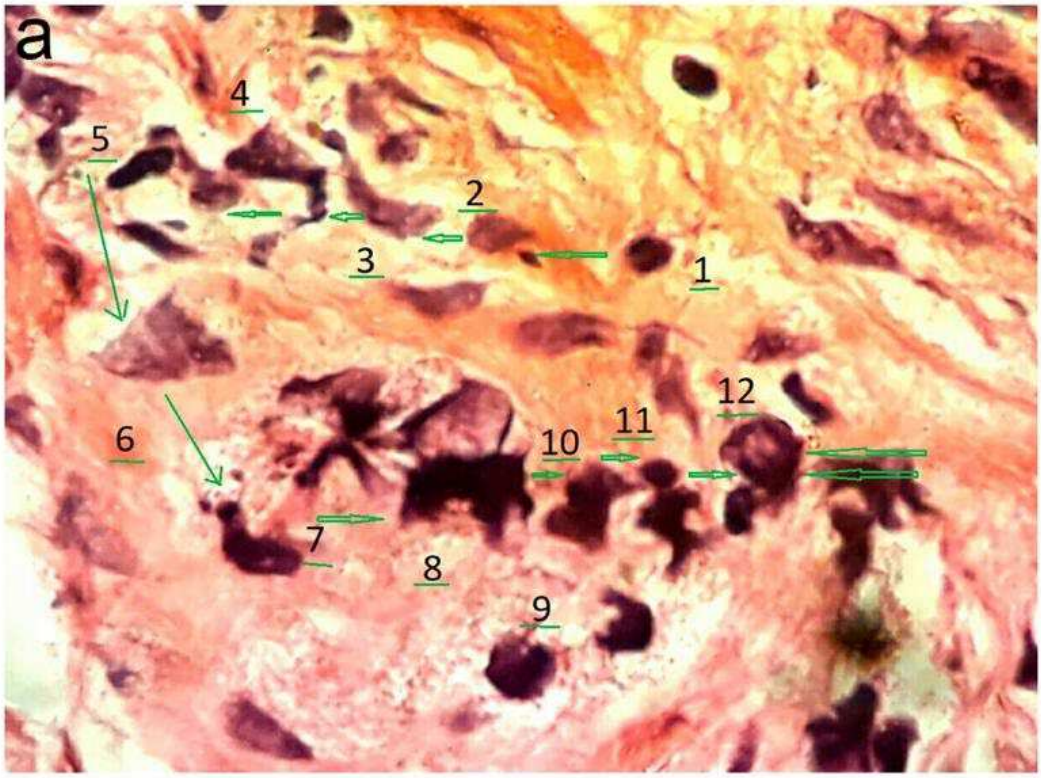


Figure 2 . Tc represents the geometric triangular spiral cleavage precursor in the formation of these embryoblast entities . We can observe how the tumor epithelial cells around Tc indicated with a red circle, have acquired the Tc phenotype , therefore behaves at distance molecular communication.

Figure 3 . panel a illustrate groups of malignant cells aligned in sequences of perfect progressive order , it is reasonable to admit that cells in stage 1 correspond to the totally undifferentiated round immature cells responsible for the highest proliferative growth, these cells are the ones that rapidly

metastasize. As the cell advances in these stages, its morphology changes, in stages 4 and 5, as observed, they become triangular with a spiral component, these cells appear more differentiated in panel b cells are positive for neuro-specific enolase their potential for tumor growth decreases. , material was captured in prostate adenocarcinoma H.E stain 40X . At stage 10, 11, 12 cells have become embryoblasts like , appear organized with a visible head-caudal polarity, these entities enter into symbiosis with the tumor host proliferatively indolent and do not metastasize . Patients who express these entities in their tumors have a longer life expectancy than those who do not express it , If we carry out DNA sequencing of stage 10, 11 and 12 cells and compare it with stage 1 DNA sequencing, probably we may find reorganization and repair of mutated DNA segments , this opens up transcendental target therapeutic possibilities in cancer


a
4
5
2
3
1
6
12
11
10
7
8
9

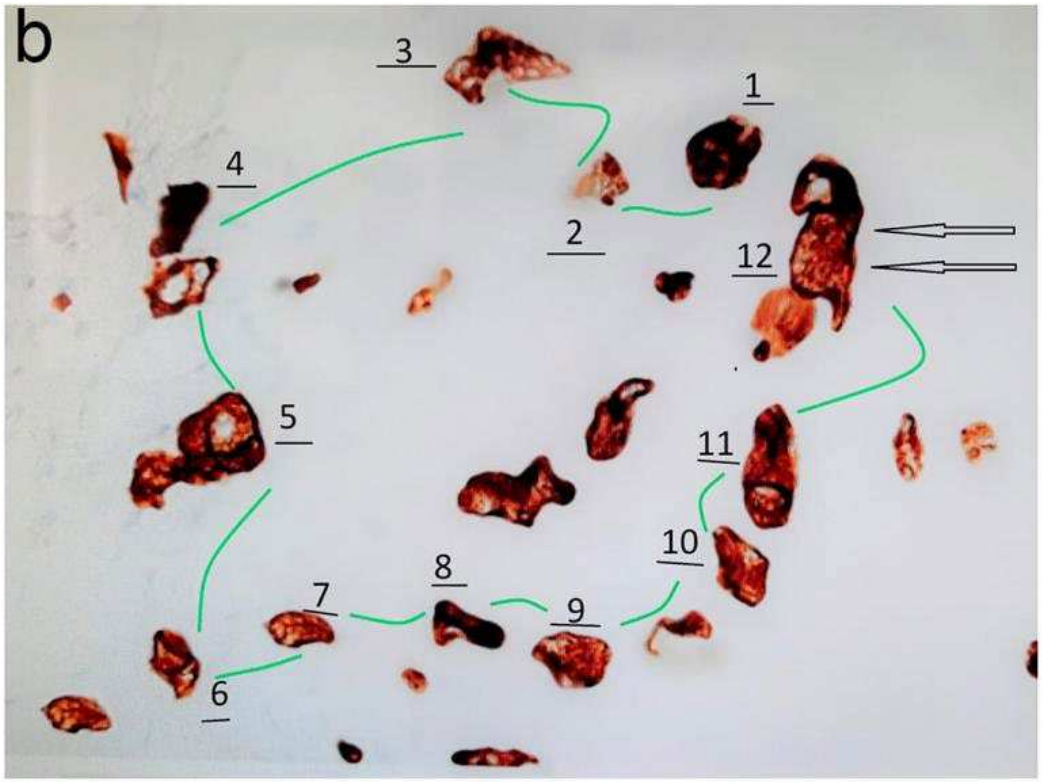

b
3
1
4
2
12
5
11
10
8
7
9
6

Figure 3. Clusters of malignant cells aligned in progressive order sequences therefore behaves at distance molecular communication , ending in the generation of an embryoblast entity

Figure 4 Shows the transfer of information from Tc to a group of tumor cells in several scenarios. Tc represents the geometric triangular - spiral cleavage **precursor** in the formation of embryoblast entities. . Material was identified in different types of malignant tumor lesions

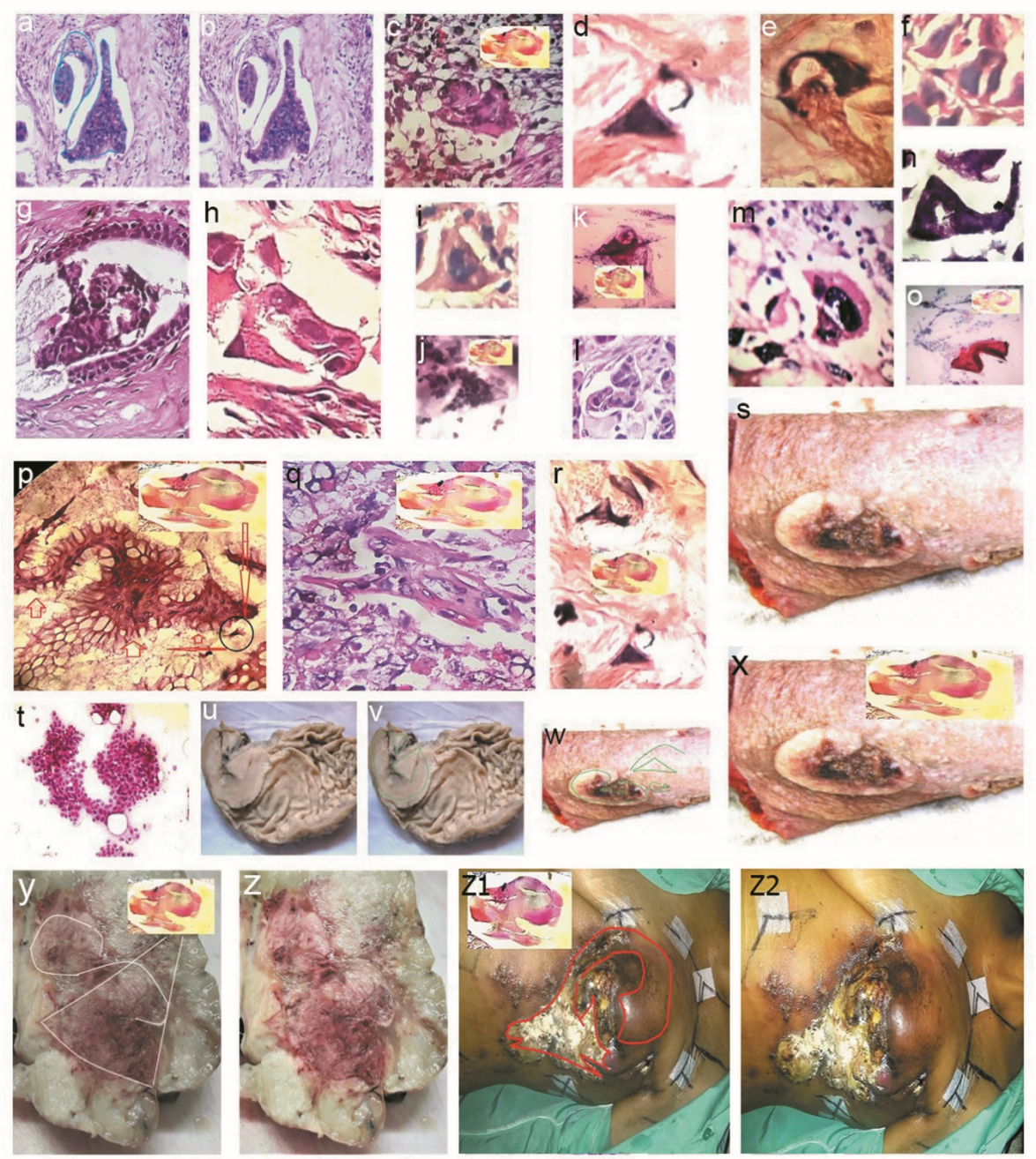


Figure 4

Transfer of information from Tc crystal protein to a group of tumor cells in different cancer scenarios

Represents the "evolutionary cycle" stage 8 and 9, the sequence in which Tc transfers information to tumor cells or groups of cells in various scenarios, changing the phenotype of the tumor cells to the crystal phenotype of Tc a,b) breast cancer HE 40 X stain. c) prostate cancer HE 40X stain. d, e , f

, g , h) breast cancer HE 40 X stain. i,j,k,l,m,n,o, lung cancer HE 40 X stain. p,q,r) colon cancer HE 40 X stain, s) macroscopic view skin cancer amputation .t, u,v) stomach cancer micro -macroscopic view . w x) macroscopic view skin cancer. y ,z) soft tissue sarcoma z1 z2) macroscopic view breast cancer.

Figure 5 shows the final stage where we can observe embryoblast- like memory entities, in different types of cancers which measure from 4 to 12 um , the hallmark of these entities is that they generate **chiral- fractal** structures as documented here with the green arrows a) breast adenocarcinoma, illustrate perfect embryoblast structures gestated by the tumor, green arrows documents chiral mirror images . b) embryoblast structure surrounded by necrotic tumor cells. Due to their differentiation, these entities resist cellular hypoxia, evade the immune system, they are probably chemotherapy and radio resistance, and paradoxically, the tumors in which these entities are identified have a better prognosis than those tumors in which they do not occur. It is logical to assume that these cells and tissues that make up this entity no longer retain tumorigenic potential or show a completely different morphology to the original tumor, with greater differentiation and less invasive growth capacity .c)Sarcoma tumor, green arrows documents embryoblast like entities with chiral mirror images . d.) Osteosarcoma e) cervical cancer cytology smear Illustrate perfect embryoblast like entity with chiral mirror image f) Brain tumor illustrate within rosette like cavity embryoblast entity with the respective chiral image .g) It is one of the most representative images where specific details of organization are recognized and not only cellular but also tissue differentiation with central vascular tubular axis , cephalo-caudal polarity. In the cephalic pole, the **temporal bone petromastoid and eye periorbital** area is recognized. Material was captured in the ascitic fluid in a patient with colon cancer. h. i) Illustrate NS high immunopositivity of embryoblast like entities .

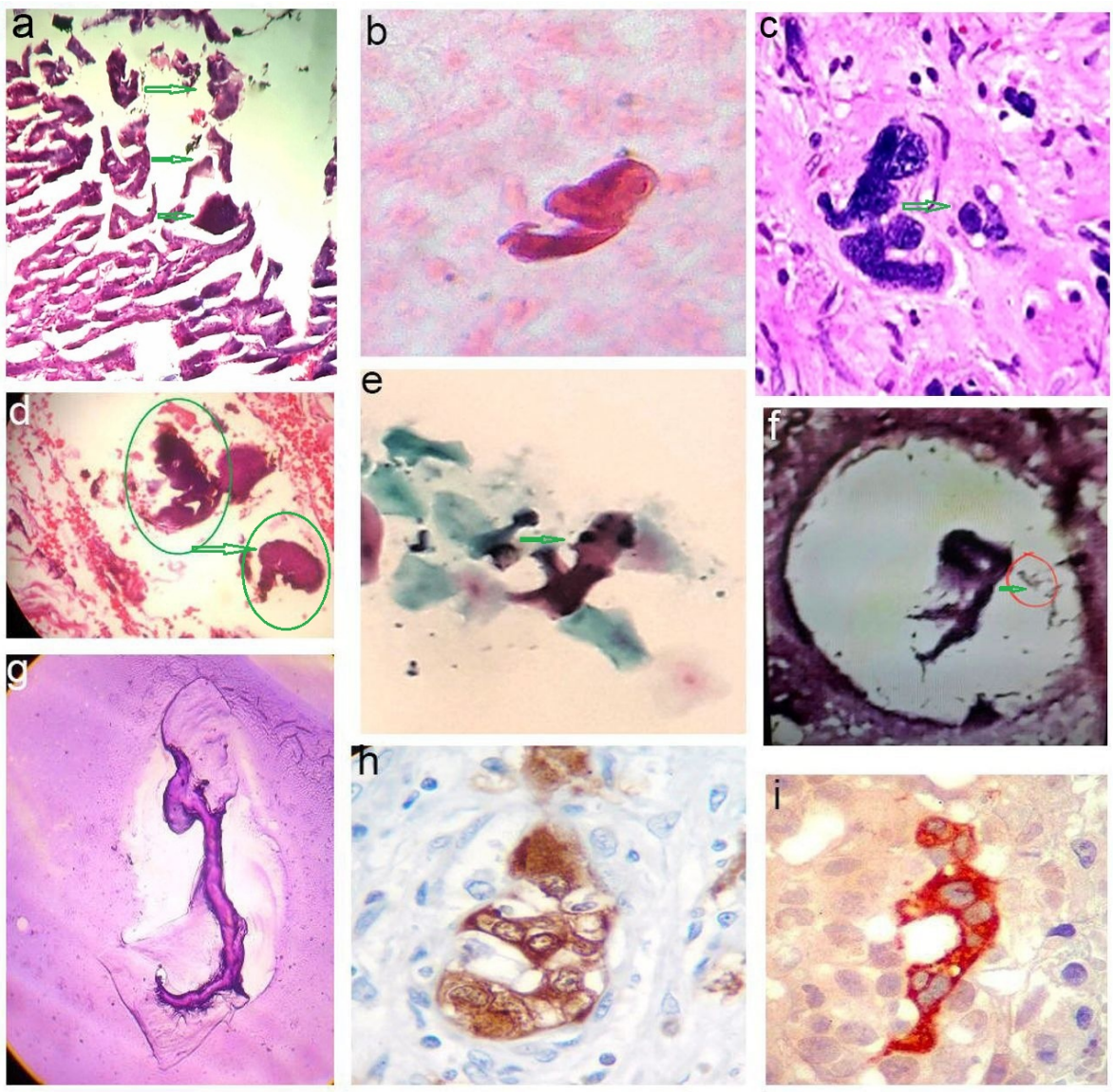


Figure 5 Evidence of cancer cell metamorphosis retrodifferentiation generating embryoblast like entities

The hallmark of these entities is that its structure can exist in two visible chiral conformations and therefore behaves at distance molecular communication which results in clusters of malignant cells aligned in progressive order sequences (green arrows).

Neuron enolase immunostaining

Tc represents the geometric triangular - spiral cleavage precursor in the formation of embryoblast entities with high immunopositivity expression for neuron specific enolase (95.0%) (table 2). (figure 3 panel b ; figure 5 panel h,)

Table 2

Analysis of neuron-specific enolase immunopositivity for Tc expression

Neuron-specific enolase		
Tc +	**Tc -**	**Final**
57	**3**	**60**
95.0%	5.0%	100%

c) **Growth memory module**

This corresponds to the macroscopic phase of the evolution of these entities that we have documented. To do this, we will rely on 7 specific cases with macroscopic and microscopic histological documentation of these cases in this phase of growth.

Case 1

Figure 6 panel a,b

a) 50-year-old patient with a brain tumor in the fronto-parietal region. Macroscopically, a large tumor lesion of 9 cm in diameter, structure with polar differentiation, can be observed; the histopathological diagnosis consisted of a glioblastoma multiforme. In panel b) we identified the microscopic crystalloid protein mold responsible for the macroscopic collective cellular memory of the tumor. We can see that they are identical.

Case 2

Figure 6 panel c

45-year-old patient with a gastric tumor with a spiral and triangulation component, macroscopic expression of Tc.

Panel d crystalloid protein microscopic mold responsible for the formation of the macroscopic collective memory mold we see in the tumor. We can observe an embryoid structure within a gastric tumor gland resembling a blastocyst-embryoblast.

Case 3

Figure 6 panel e, f

56-year-old male patient with a gastric tumor diagnosed as a well-differentiated gastric adenocarcinoma. The surgical specimen shows an unusual pattern with clear cephalo-caudal differentiation with the presence of a defined optic cup. The e panel shows the microscopic crystalloid memory of this tumor**.** Panel f shows an embryoblast like structure within a tumor gland resembling a blastocyst-embryoblast.

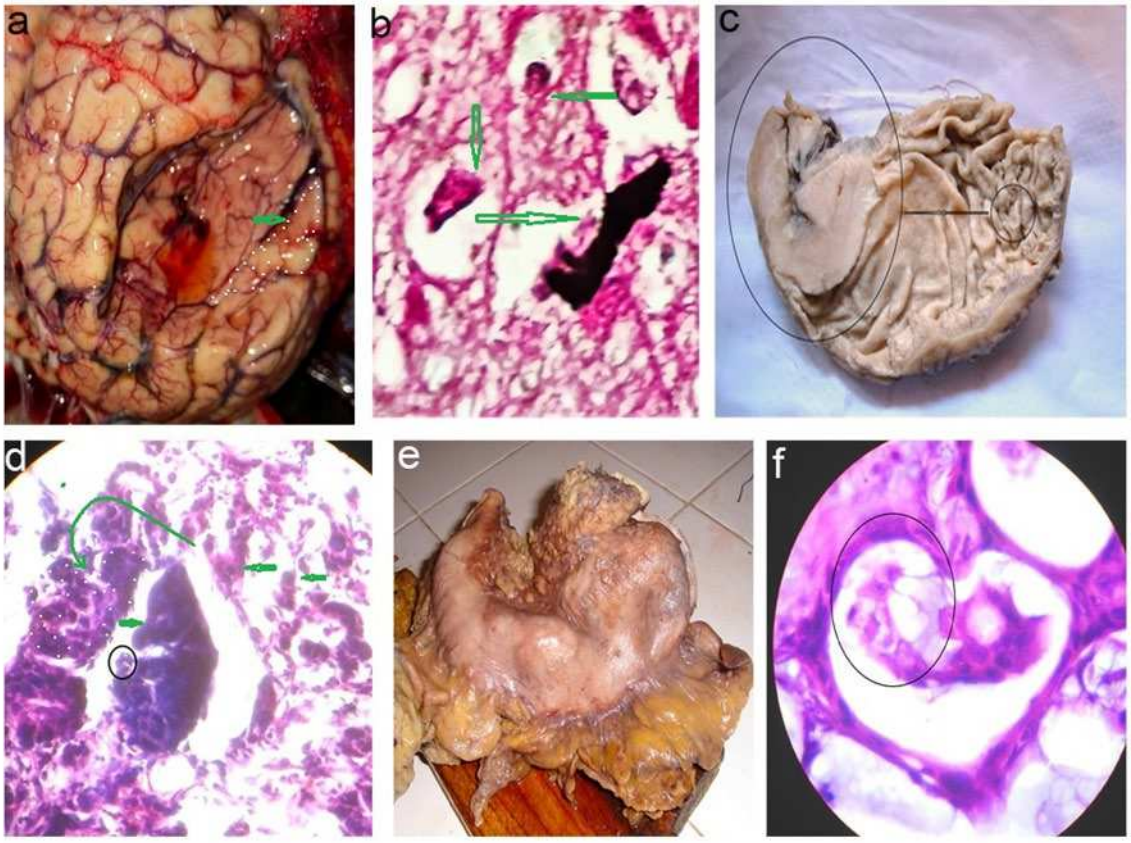


Figure 6

Glioblastoma multiforme l a) macroscopic phenotype lesion b) microscopic phenotype lesion, it can be seen how the two phenotypes are identical. Panel c,d) gastric cancer, the microscopic crystalloid phenotype is identical to the macroscopic tissue phenotype. Millions of copies of an individual microscopic crystalloid memory generate a collective macroscopic memory identical to the microscopic one in time (8 to 9 years) through the transfer of information, panel e,f) gastric cancer macroscopic phenotype identical to the microscopic phenotype

Case 4

Figure 7 a,b

80-year-old patient with a breast tumor. We can see a giant tumor lesion. In panel b the microscopic study of this lesion showed a lesion with a bilaminar component identical to the one observed macroscopically. We can clearly see an embryoid structure that is assembled from the cells detached

from the epithelium of the breast tumor gland, resembling a blastocyst-embryoblast. The microscopic seed grew in time, generating identical fractal copies that originate the pattern of the macroscopic tumor.

Case 5

Figure 7 c, d

50-year-old patient with a uterine leimiosarcoma, a surgical specimen weighing 3500 grams of cerebroid appearance, measuring 20 x 18 x 19 cm. A nest-like lesion was identified in the central region where 2 triangular structures can be seen in a chiral position in a mirror image with a spiral component inside them. Panel c shows 2 structures with , one structure on the left of embryoid pattern with a feminine appearance due to the curvilinear morphology and on the right side another structure with less curvilinear morphology with a masculine appearance. , in the microscopic findings we identify the microscopic seed of this macroscopic twin structure (panel d)

Case 6

Figure 7 e, f

A 35-year-old male patient with a tumor lesion in the small intestine. Panel e shows the surgical specimen with a highly unusual morphology, where there is a structure with a polar cephalic pattern as well as a caudal pattern. Panel f shows the microscopic clusters of malignant cells aligned in progressive order sequences that generates the macroscopic pattern.

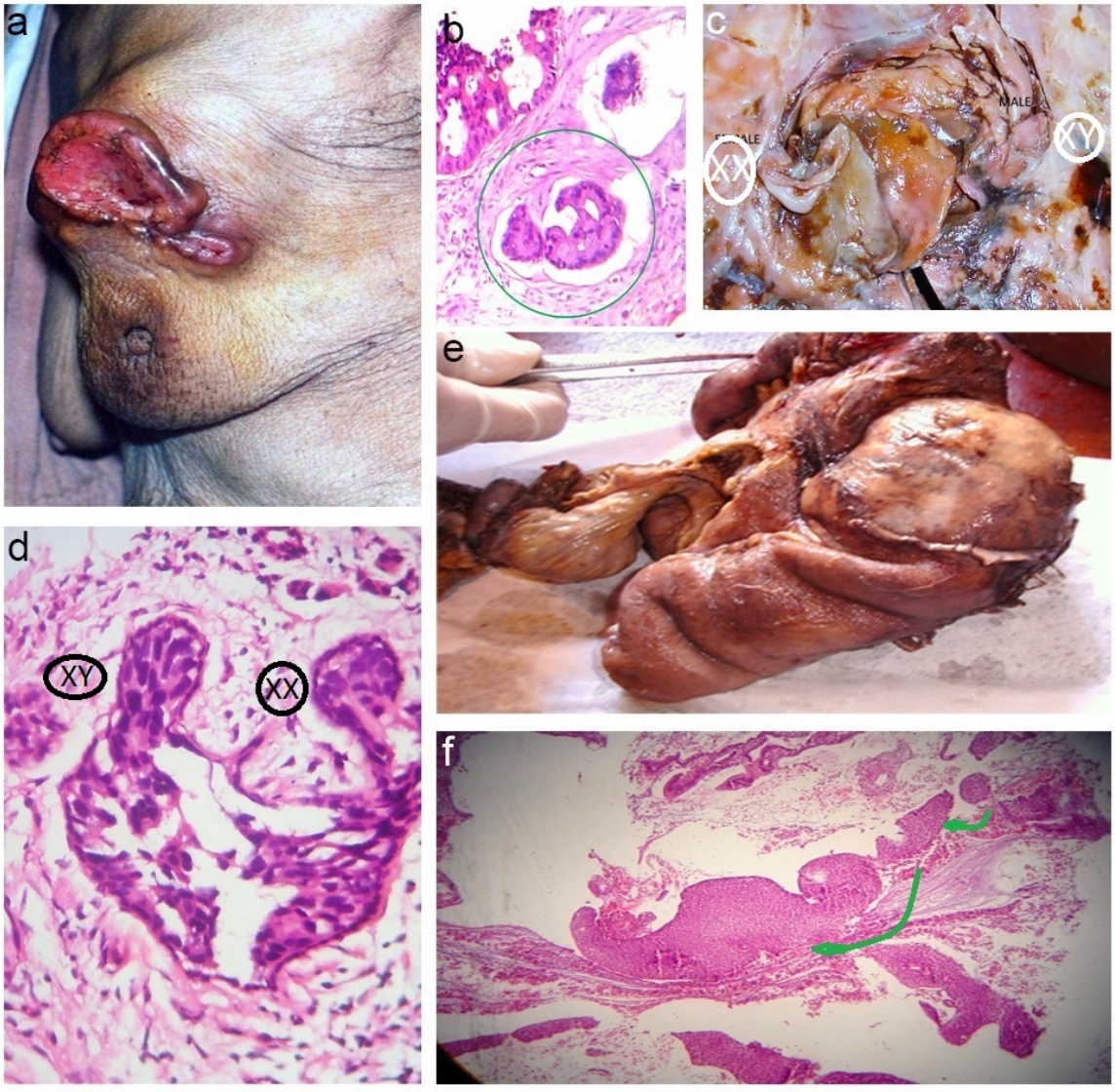


Figure 7

a, b . 80 year-old patient with a breast tumor. A giant breast tumor lesion can be seen that clearly shows an unusual morphology of cephalo-caudal pattern with an upper base and a lower base that is also triangular with a bilaminar caudal portion. The microscopic study of this lesion showed an identical lesion with a bilaminar component identical to the one observed macroscopically. The microscopic seed grew in time generating millions and millions of macroscopically identical fractal copies. c, This is a 50 year old tumor patient with a uterine leiomyosarcoma, panel c, a nest-like lesion where 2 triangular structures are seen in a mirror image in chiral position with a spiral

component, 2 structures are seen with caudal-cephalic characteristics on the left in appearance embryoblast **XX phenotype** pattern due to the curvilinear morphology of its lines, on the right side is another less curvilinear morphology structure with **XY phenotype** pattern d) illustrates another microscopic embryoblast like entity with two visible chiral conformations : XY and XX phenotype patterns side to side. Material was captured in breast adenocarcinoma. H. E stain 40 x. e, f) Small intestine lymphoma, the microscopic phenotype iidentical to the macroscopic phenotype,

Case 7

Figure 8 a, b, c, d, e, f

A 35-year-old male patient with a retroperitoneal tumor lesion measuring 25 cm in length and weighing 2800 grams. Panels a, b, and c show the perfect tracing that we were able to carry out in this case. Panel a shows how the individual microscopic memory has its genesis inside a tumor gland from a molecular liquid that solidifies and crystallizes. Panels b and c irrefutably illustrate stages 1 to 7 where the spontaneous configuration of embryoblast -like entities is shown, **clear biomimicry of the human blastocyst**. Millions of copies of this microscopic crystalloid memory generated an entity with clear fetal characteristics in a period of 8 to 9 years. Panels d and e show the result of this replication in time, a macroscopic fetal structure in profile and from the front. Panel f shows a cross section of the characteristics of the tumor that was diagnosed as a component of a carcinomatosis with origin in the sigmoid colon.

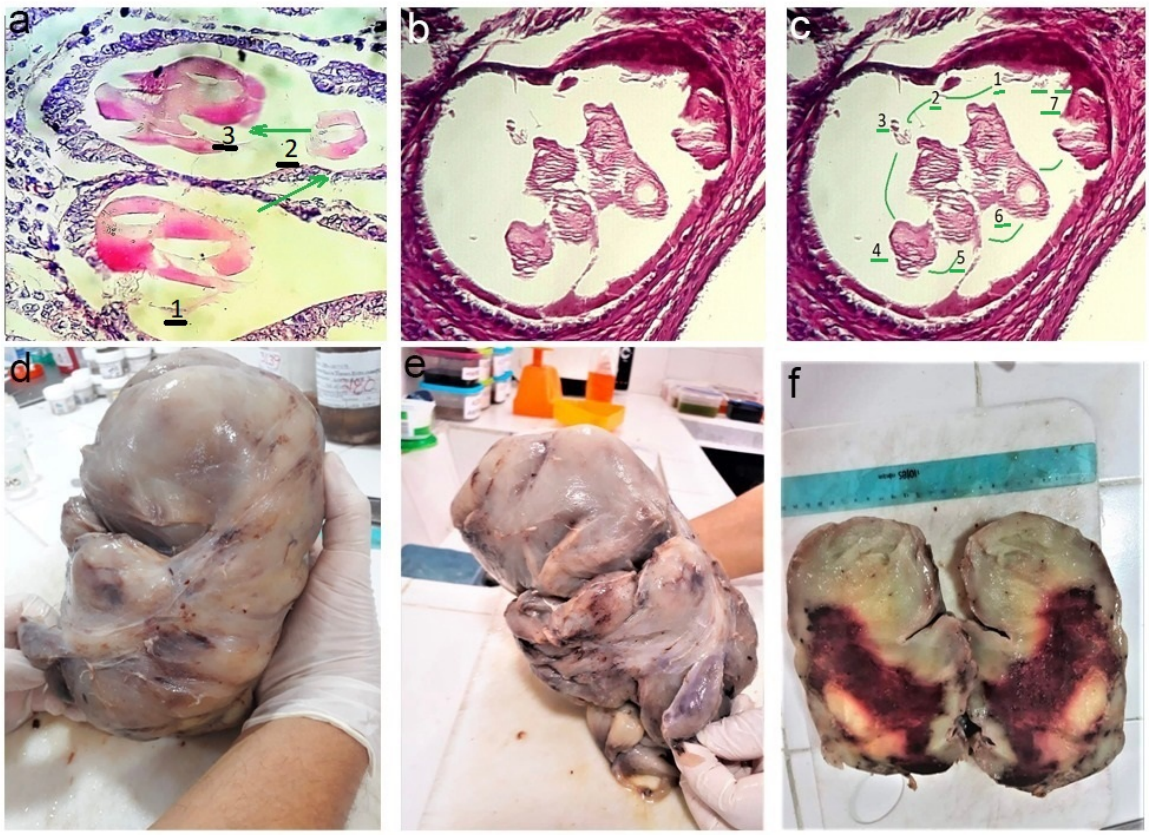


Figure 8 a, b, c, d, e, f) This is a 35-year-old male patient with a retroperitoneal tumor lesion measuring 25 cm in length and weighing 2800 grams. Panels a, b, and c show the perfect tracing that we were able to carry out in this case. Panel a shows how the individual microscopic memory has its genesis inside a tumor gland from a molecular fluid that solidifies and crystallizes. Panel b,c irrefutably illustrates in stages 1,2,3,4,5,6,7 how the fluid secreted by the tumor epithelial cells solidifies and becomes crystalloid. From this individual crystalloid memory an easily discernible embryonic phenotype is sequentially formed in stages 3 to 7. Copies of this microscopic crystalloid memory generated an entity with clear fetal-type characteristics over a period of 8 to 9 years, identical to the crystalloid memory phenotype that served as the mold. Panel d,e, shows an almost perfect fetal macroscopic structure in profile and from the front, panel f shows a cross-section of the characteristics of the tumor that was diagnosed as a component of a sigmoid colon carcinoma.

Figure 9 a, b,

Illustrate embryoblast entity with perfect visualization of **shape hand plate** represented by digital rays as a result of apoptotic cell death within interspaces, we are observing anatomical position with a 90 degree rotational axis that shows bone and cartilaginous differentiation. this limb bud was documented from the metamorphic retrodifferentiationn of cancer cells,and was capture in observable event of limb bud formatio in breast adenocarcinoma, additionally the photomicrograph illustrate hand -mouth interconnection contact similar to that observed in an embryo of 6 to 10 weeks indicating integration between different motor sensory systems, potential factor of prenatal development

c, d

Initial experiments in our laboratory show that we can artificially reproduce the assembly of these embryoblast-like entities by inducing slight controlled physical-chemical stress on the epithelium of minor salivary glands in healthy young individuals, as shown in the images**. Expression of dormant genes can be induced by artificial stimulation.**

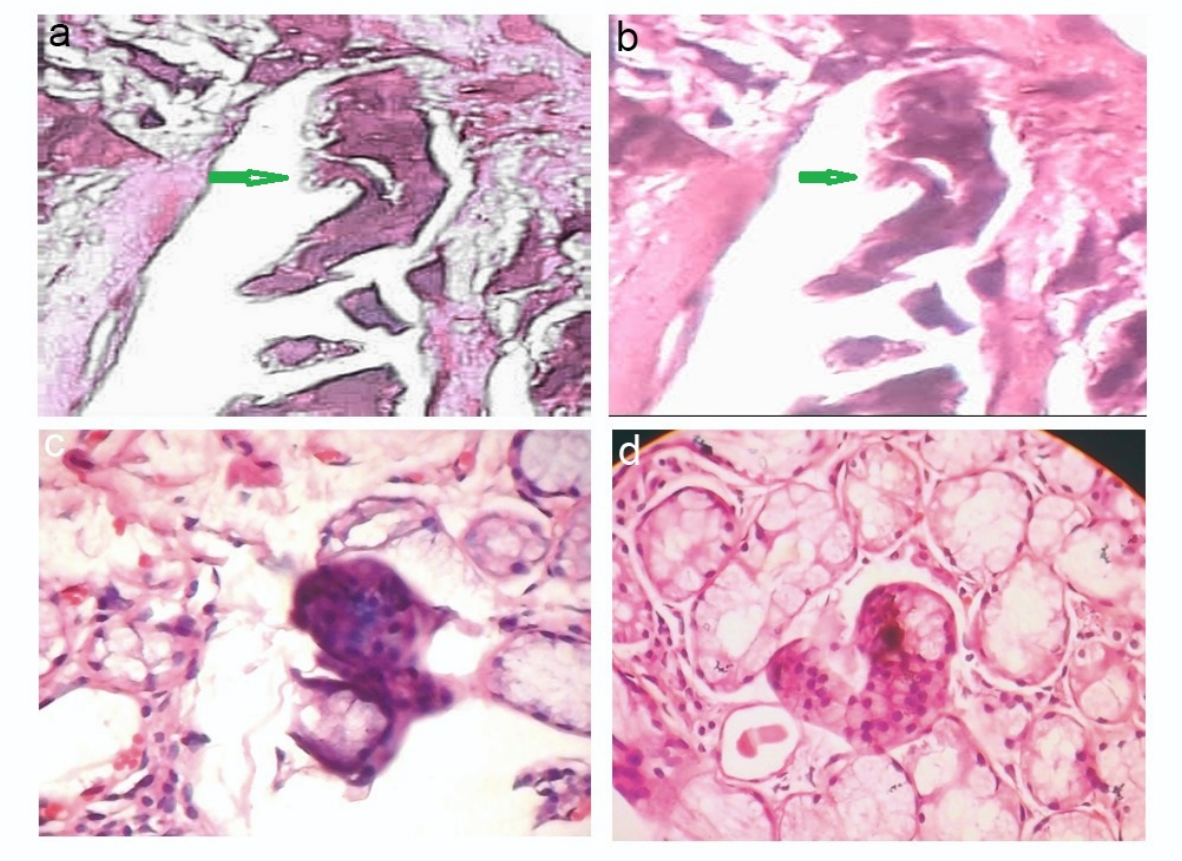


Figure 9.

Evidence of cancer cell metamorphosis retrodifferentiation

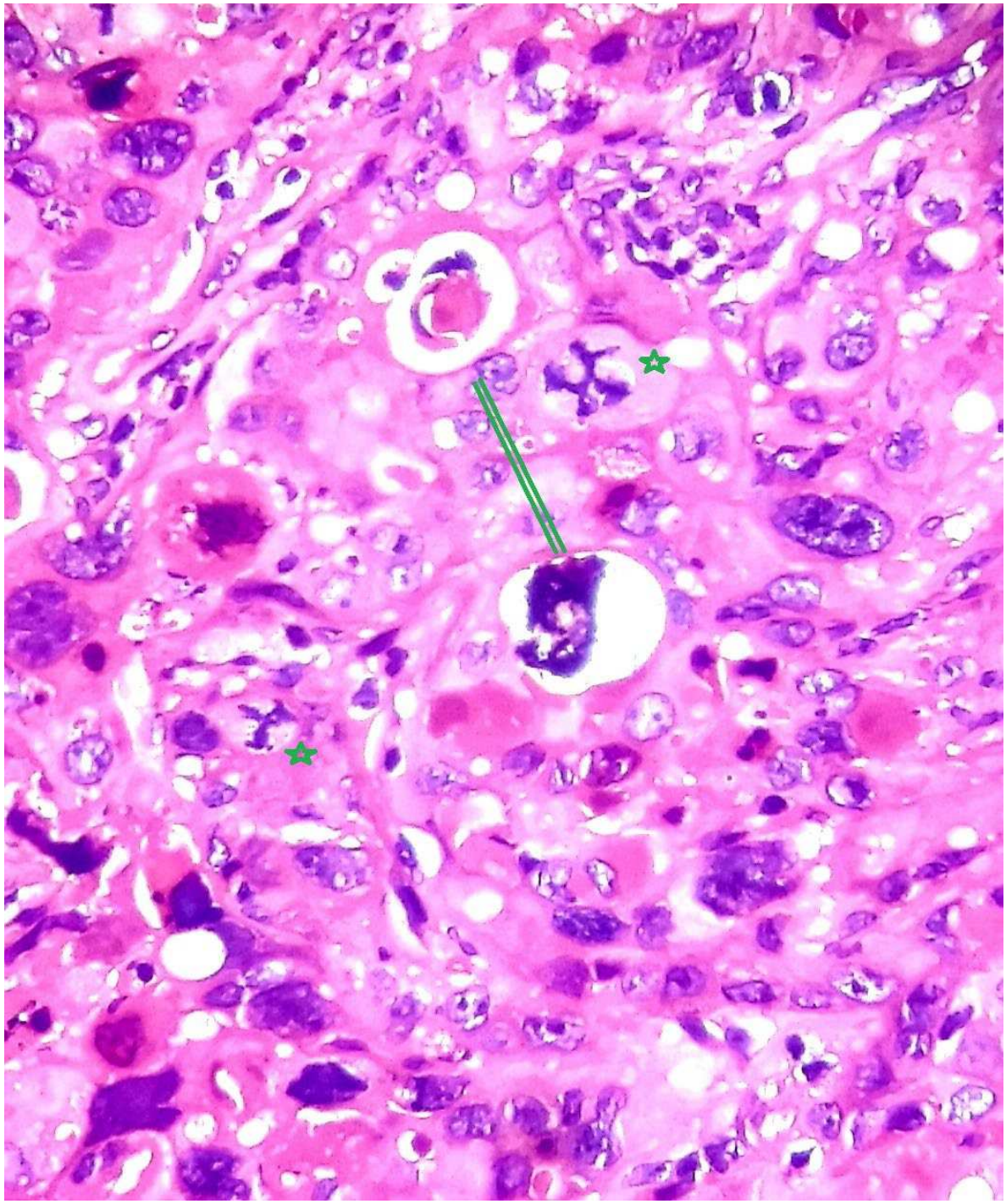


Figure 10

Image illustrates an aggressive squamous cell malignant tumor with great cellular pleomorphism and atypical mitosis*, in the middle of the field , arises an embryoblast-like structure with vestiges of incontrovertible upper and lower limbs , located within a blastocyst -like cavity with the

registered hallmark of these entities: generating a mirror image. In tumor biology extreme disorder via cellular injury, mutations, viruses and cellular senescence generates via retrodifferentiation extreme biological order - embryoblast like entities.

DISCUSSION

For the skeptical observer, these entities may appear fixation, cut or staining artifacts dependent on the histological technical process, below we offer verifiable reasons that show how these entities are real predictable and reproducible entities :

a) These entities appear in states of cellular emergency and do not appear in normal tissues

b) Represent the product of an organized process of sequential metamorphic retrodiferentiation in which malignant cells line up in a progressive architectural order.

c) The cells that make up these entities show neuroectodermal differentiation and are positive for NSE

d) The hallmark of these entities is that its structure can exist in two visible chiral conformations and therefore behaves at distance molecular communication which results in clusters of malignant cells aligned in progressive order sequences fig 5 (green arrows) what involves apical- basal polarization , cell adhesion, cell communication , spatial migration programmed apoptosis and positional signals; Behind the morphogenesis of these entities appear prepattern of crystalloid protein ,precursors of geometry that we call Tc .

e) These entities have micro and macroscopic grow representativeness , may show bone and vascular tubule differentiation fig 5g . Oral and manual activity , Integration between different sensorymotor systems similar to the early stage of fetal development, 8- 9 weeks of gestational age, figure 9 a.b

f) Figure 7d illustrates embryoblast like entity with two visible chiral conformations : XY and XX phenotype patterns side to side.

g) These structures resist the normal tumor necrosis activity suffered by the tumors, as seen in

the figure 5b where an embryoblast like entity is observed in the middle of tumor necrosis.Verifying as well as these entities are resistant to the cytolytic immune system and probably to the action of chemo and radiotherapy.

h) These entities are perfect microscopic versions of a 10 to 13 week old human embryo

i) Emerge within glandular structures or in areas of cystic degeneration mimicking the fluid-filled blastocyst cavity during embryogenesis

j)These entities eliminate all the proliferative power growth from the tumor as they differentiate neuroectodermally, entering into symbiosis with the host preventing metastasis and determining a better prognosis for tumors that express these entities compared to those that do not present them.

k) In tumor biology extreme disorder via cellular injury, mutations, viruses and cellular senescence generates via retrodifferentiation extreme biological order - embryoblast like entities Fig 10.

k) finally we were able to generate these “artifacts” Initial experiments in our laboratory show that we can artificially reproduce the assembly of these embryoblast-like entities by inducing slight controlled physical-chemical stress on the epithelium of minor salivary glands in healthy young individuals, as shown in the images. Expression of dormant genes can be induced by artificial stimulation fig 9 c.,d

Clearly these entities are not artifacts. It is the organization of a group of cells that were previously disorganized , an amorphous tumor and now under the expression of dormant genes of the embryogenesis, has absolutely amazing characteristics of an embryoblast like structure

Biology gives us a practical lesson with these entities the probably only way to repair, correct and regenerate tissue is ” Go Back” by recapitulating early stages of embryogenesis by awakening dormant genes.

Refusing to accept what is clearly observed in repetitive patterns in different settings is to deny autonomy to deductive reasoning and this harms science, immobilizes it and does not generate new knowledge

The main characteristic of these entities is the identification of clusters of malignant cells aligned in perfect progressive order sequences Sequence clustering attempt to group biological sequences that are somehow related. constructing a transitive closure of sequences with a similarity. The similarity is often based on sequence alignment. These progressive linear sequences makes us remember a linear sequence of nucleotides along a segment of DNA that provides the coded instructions for synthesis of RNA, which, when translated into protein, leads to the expression of phenotype character . Cells aligned in progressive order sequences then it must correspond to a molecular guideline of assembly information of genes and DNA. Knowing the DNA sequence ordering in these entities would have transcendental practical and therapeutic applications.

These patterns of sequentiality and order show that in the midst of the biological chaos and mutations that cancer represents, there is a product in development that is "gestating" as a result of the reactivation of signals from genes and proteins that return from embryogenesis.

we are facing probably with an emergent evolutionary biological response, we postulated that these entities that we are documenting are not there randomly, they have a function with the capacity to repair modify and or regenerate damaged senescent and mutated cells.

The **genesis** of these entities is given by the **fluid** secretions of the tumor glands that spin in the opposite direction, and solidify forming crystals of spiral triangular geometry, representing the crystalloid structural protein of these entities, which measure just a few microns but acquire polarity, organize, fuse and generate a triplet of triangular images and spirals forming a conglomerate that we have called triplet crystal (Tc). **Tc represents the geometric triangular - spiral cleavage precursor in the formation of these embryoblast like entities**.

.

In articles such as Magnetization of the three-spin triangular Ising model, theoretical physicists have already used mathematical formulas to address the organizing power of these geometric conglomerates, that take shape now in cancer biology and become real in practice in these self-

organizing entities that we have documented here for the first time. **Tc** is a new, unique structure that nature builds at the interface of physics and biology where **Geometric spin systems hold promise for finding new phases of biological self-assembly**. [16 17]

The theory of physics of a magnetization model forming a perfect conglomerate of a three-spin, three-triangle triplet is shown in the figures of the paper. In detail, a slender crystal-like Tc is able to behave as a vector of biological information and transmit its phenotype to squamous cells that change their phenotype in response to this transmitted information. As we can clearly see in the "evolutionary cycle" these cells slowly and progressively change their phenotype, turning into a final product; embryoblast memory entities. This visible transfer of information from Tc to the tumor cells reminds us of the hypothesis of Professor Cairns-Smith, A. G when he states that crystals can behave as genes mainly in relation to cancer. (18)

What are these entities and what do they represent? **We can see how the traces of the initial phase of development of blastocyst-embryoblast are indelibly engraved and stored forever in the individual and collective memory of all the normal cells of the human body** which we believe represent the genetic basis of tissue regeneration and repair, as mainly observed in the glandular epithelium, a memory that is activated in a state of cellular emergency, disorganization or cellular senescence. Perfect microscopic replicas of morphological information that possess the information of a collective memory encoded in its nucleus and anchored to the period of embryogenesis. Every cell that is irreversibly injured and escapes programmed cell death or apoptosis has the plasticity of metamorphosis and the ability to return to an embryonic stage. This translates into a transcendental biological fact: Every cancer cell returns partially or totally to an embryonic genotype-phenotype,

This article is the consolidation of over 10 years of work [19. 20]. **A recent publication in an animal model by researchers from the neuroscience department of the University of California support our findings in human tissues, as they found that adult neuronal cells in mice exposed to cell damage return to a state of embryonic transcriptional growth state [21].** These findings are of unquestionable crucial significance for our research: These authors identify the transcriptional traces of embryonic growth, our group documents the entity that generated these traces, which

determines that the methodology we used and the data we collected are reliable to the point that they can be reproduced and predicted in other laboratories around the world.

The hypothesis linking cancer and cell damage to embryogenesis is not new, Cohnheim suggested in 1882 [22] that tumor cells were essentially "embryonic" in nature, being remnants of embryonic epithelial cells. In the early 1970s, Brinster [23] demonstrated that by injecting embryonic carcinoma cells into a mouse blastocyst, the mouse was able to regulate the cancer cells and their progeny to the point that they no longer behaved malignantly; rather, they participated in normal embryonic development that resulted in functional mice. This experiment was confirmed by Mintz and Illmensee [24] and Papaioannou [25]. Pierce [26,27], showed that this effect, specific for some types of tumor cells, is strongly position-dependent: the carcinoma cells placed between the pellucid zone and the trophytoderm (the perivitelline space) were not controlled, while the carcinoma cells injected into the blastocele lost their tumorigenicity immediately after differentiation. Clinical trials, conducted with zebrafish embryo extracts administered to patients with advanced cancer that did not respond to conventional treatments, significantly reduced the expression of oncofetal antigens (such as AFP) [28] and induced marked beneficial effects (induction of objective responses, improvement in state performance and significant increase in overall survival) [29-31] .

Additionally, our morphological findings fit perfectly with the new hypothesis by molecular biologist Jose A from the University of Maryland who states that DNA is only "the list of ingredients" and not the set of instructions used to build and maintain a living organism. These instructions are very complex and are stored inside each individual cell as a shape memory that "decides" how and to what extent to use the ingredients available in the DNA. "DNA cannot be seen as the 'blueprint' for life" [32 33].

According to Dr. Jose the fundamental aspects of anatomy are dictated by something outside of DNA and he proposes that non-coding instructions in DNA are actually contained in the architectural arrangement of molecules within cells and in the interactions between them. This arrangement (shape memory) is what is preserved and transmitted from one generation to the next**.**

The findings of our study agree with the observations of Jose *et al* from the perspective that the entities found have their own identity and are unique since they have the differential phenotype of the host where they were gestated. In addition, the presence of visible pores or perforations also reported in the basement membrane of mouse embryos [Kyprianou et al [34] is noteworthy,

supporting the theory that the entities found by us present characteristics of real “microscopic” embryos.

The analysis of living systems from molecular to population scales has revealed how the storage and processing of information across multiple scales is a key attribute of life, in which order can arise through the spontaneous association of molecules in the living system and the formation of dynamic structures (Tc) that can store and retrieve information from collections of self-assembled and self-organized molecules. These different ways of changing entities, sensors and properties highlight the multi-scale nature of living systems and suggest the usefulness of different entity-sensor-property frameworks at different molecular-microscopic-macroscopic scales that cannot be explained solely from the perspective of DNA or genome analysis.

,

Our findings document how malignant tissues reactivated ancestral storage memory and elaborate, crystalline proteins repaired copies of the damaged substrate tissue. The resultant embryoblast template probably guides and controls the regenerative pathway mechanism in human tissues as follows: 1) Modify and reprogram the phenotype of the tumor where these entities are generated. 2) Establish a reverse primordial microscopic mold to use the collective behavior of cellular building blocks to regenerate injured tissues. 3) Convert cancer cells to a normal phenotype by developmental patterning of active patterning cues. 4) Convert cancer cells to a normal phenotype by regeneration using the organizational level and scale properties of reverse genetic guidance. 5) Globally control mitotic activity and morphogenetic movements avoiding their spread and metastasis, determining a better life prognosis for patients who incubate these entities in their tumors compared to those who do not express them.

These images clearly express, as never before, how a geometrical ordering entity (Tc) can somehow physically regulate the micro-macro cellular environment where these entities are gestated. We can predict these structures based on the knowledge of microscopic forces of self-assembly. At present, there is no documented structure produced naturally, where this structural conjunction between physics and biology is so clear and perfect, which makes it a real platform to be copied and used in the assembly and design of new proteins and artificial biostructures.

. These observations confirm the importance of the foetal characteristics of cancer as a source of

useful information that can contribute to better understanding of the biology of cancer at molecular, cellular and micro-environmental levels.

Finally we believe that these isolated collective cellular entities are ready to be removed from their tumor microenvironment, as a product that has reached its maturity and has completed a cycle and is waiting to be used to develop new target therapeutic alternatives not only in cancer but also in treatment of autoimmune, viral diseases, in regenerative medicine and rejuvenation**.**

Acknowledgements

The authors thank the board of directors and authorities of the Departmental Hospital of Villavicencio Meta and Dr Jesus Emilio Rosado, director of the Departmental Hospital of Granada Meta) for financial and logistical support in the realization of this project.

Authors' contributions

J.A.D., L.S , and L. A. D guided the project, wrote the paper and analysed the results. M.F.M L.C.P K.T.M., O. F. S., M. A.C. and L.K.S recollected and processed the samples.

Competing interests

The authors declare that they have no conflicts of interest.

References

1. White, C. P. On the occurrence of crystals in tumours. J. Pathol. Bacteriol. 13, 3–10 (1909).

2. Rose, G. G. Biologic Crystals and Particles Produced in Tissue Culture. Cancer Res. 24, 1159 LP-1193 (1964).

3. Díaz, J. A., Jaramillo, N. A. & Murillo, M. F. Geometric Triangular Chiral Hexagon Crystal-Like Complexes Organization in Pathological Tissues Biological Collision Order. PLoS One 2, e1282 (2007).

4. Díaz, J. A., Murillo, M. F. & Jaramillo, N. A. Framework of Collagen Type I – Vasoactive Vessels Structuring Invariant Geometric Attractor in Cancer Tissues: Insight into Biological Magnetic Field. PLoS One 4, e4506 (2009).

5. Diaz, J. & Murillo, M. F. Phenotype characterization of embryoid body structures generated by a crystal comet effect tail in an intercellular cancer collision scenario. Cancer Manag. Res. 9 (2012). doi:10.2147/CMAR.S25810

6. Lee, J., Abdeen, A. A., Wycislo, K. L., Fan, T. M. & Kilian, K. A. Interfacial geometry dictates cancer cell tumorigenicity. Nat. Mater. 15, 856–862 (2016).

7. Tozluoğlu, M. et al. Matrix geometry determines optimal cancer cell migration strategy and modulates response to interventions. Nat. Cell Biol. 15, 751–762 (2013).

8. Roy, B. et al. Laterally confined growth of cells induces nuclear reprogramming in the absence of exogenous biochemical factors. Proc. Natl. Acad. Sci. 115, E4741–E4750 (2018).

9. Ma, Y. et al. The relationship between early embryo development and tumourigenesis. J. Cell. Mol. Med. 14, 2697–701 (2010).

10. Lee, J. T. & Herlyn, M. Embryogenesis meets tumorigenesis. Nat. Med. 12, 882–884 (2006).

11. Behrens, J. & Lustig, B. The Wnt connection to tumorigenesis. Int. J. Dev. Biol. 48, 477–487 (2004).

12. Moll, U. M. & Slade, N. p63 and p73: roles in development and tumor formation. Mol. Cancer Res. 2, 371–86 (2004).

13. Chen, C.-M. Ovca1 regulates cell proliferation, embryonic development, and tumorigenesis. Genes Dev. 18, 320–332 (2004).

14. Studer, L. et al. Enhanced proliferation, survival, and dopaminergic differentiation of CNS precursors in lowered oxygen. J. Neurosci. 20, 7377–83 (2000).

15. Perryman, S. V & Sylvester, K. G. Repair and regeneration: opportunities for carcinogenesis from tissue stem cells. J. Cell. Mol. Med. 10, 292–308

16 Magnetization of the three-spin triangular Ising model R J Baxter et al 1975 J. Phys. A: Math. Gen. 8 245

17 XXZ and Ising spins on the triangular kagome lattice PHYSICAL REVIEW B 78, 024428 2008 Dao-Xin Yao, Y. L. Loh, and E. W. Carlson

18 Cairns-Smith, A. G. The origin of life and the nature of the primitive gene. J. Theor. Biol. 10, 53–88 (1966).

19 Díaz, J. A., Murillo, M. F. & Barrero, A. Intercellular cancer collisions generate an ejected crystal comet tail effect with fractal interface embryoid body reassembly transformation. Cancer Manag. Res. 3, 143–55 (2011).

20 Diaz, J. A. Murillo, M. F. Mendoza,A . Barreto,A.M. Poveda,L,S. Sanchez,L.K. et al . Human somatic cells acquire the plasticity to generate embryoid-like metamorphosis via the actin cytoskeleton in injured tissues. Am. J. Stem Cells 5, 53–73 (2016).

21 Poplawski, G.H.D., Kawaguchi, R., Van Niekerk, E. et al. Injured adult neurons regress to an embryonic transcriptional growth state. Nature 581, 77–82 (2020). https://doi.org/10.1038/s41586-020-2200-5

22 Cohnheim, J. In: Lectures in General Pathology; Translation by McKee, A.B. New Sydenham Society, London, 1889.

23 Brinster, R. L. The effect of cells transferred into the mouse blastocyst on subsequent development. J. Exp. Med., 1974, 140, 10491056.

24 Mintz, B.; Illmensee, K. Normal genetically mosaic mice produced from malignant teratocarcinoma cells. Proc. Natl. Acad. Sci. USA, 1975, 72, 3585-3589.

25 Papaioannou, V. E.; McBurney, M. W.; Gardner, R. L.; Evans, R. L. Fate of teratocarcinoma cells injected into early mouse embryos. Nature, 1975, 258, 70-73.

26. Pierce, G. B. The cancer cell and its control by the embryo. Rous-Whipple Award lecture. Am. J. Pathol. 113, 117–24 (1983).

27 Pierce, G. B.; Lewis, S. H.; Miller, G. J.; Moritz, E.; Miller, P. Tumorigenicity of embryonal carcinoma as an assay to study control of malignancy by the murine blastocyst. Proc. Natl. Acad. Sci. USA, 1979,

28 Franchi, F.; Ielapi, T.; Bizzarri, M.; Seminara, P. Embryo extracts opotherapy reduces a-fetoprotein levels in hepatocellular carcinoma patients. J. Gastroent. Hepatol., 2005, 20, 1464-1473. [29 Livraghi, T.; Meloni, F.; Frosi, A.; Lazzaroni, S.; Bizzarri, M.; Frati, L.; Biava, P. M. Treatment with stem cell differentiation stage factors of intermediate-advanced hepatocellular carcinoma

30 Bizzarri, M.; Facco, R.; Ielapi, T.; Frati, L. The embryonic and maternal regulatory factor as a palliative therapy for advanced solid tumours. J. Tumour Marker Oncol., 2002, 17(3), 31-36

31 Biava, P. M.; Fiorito, A.; Negro, C.; Mariani, M. Effects of treatment with embryonic and uterine tissue homogenates on Lewis lung carcinoma development. Cancer Lett., 1988, 41, 265-270.

32 Antony M. Jose framework for parsing heritable informationJ. R. Soc. Interface.17: 2020 0154

33) Antony M. Jose Heritable Epigenetic Changes Alter Transgenerational Waveforms Maintained by Cycling Stores of Information. BioEssays 2020 https://doi.org/10.1002/bies.201900254

34 Kyprianou, C., Christodoulou, N., Hamilton, R.S. et al. Basement membrane remodelling r

egulates mouse embryogenesis. Nature (2020). https://doi.org/10.1038/s41586-020-2264-2

Figures

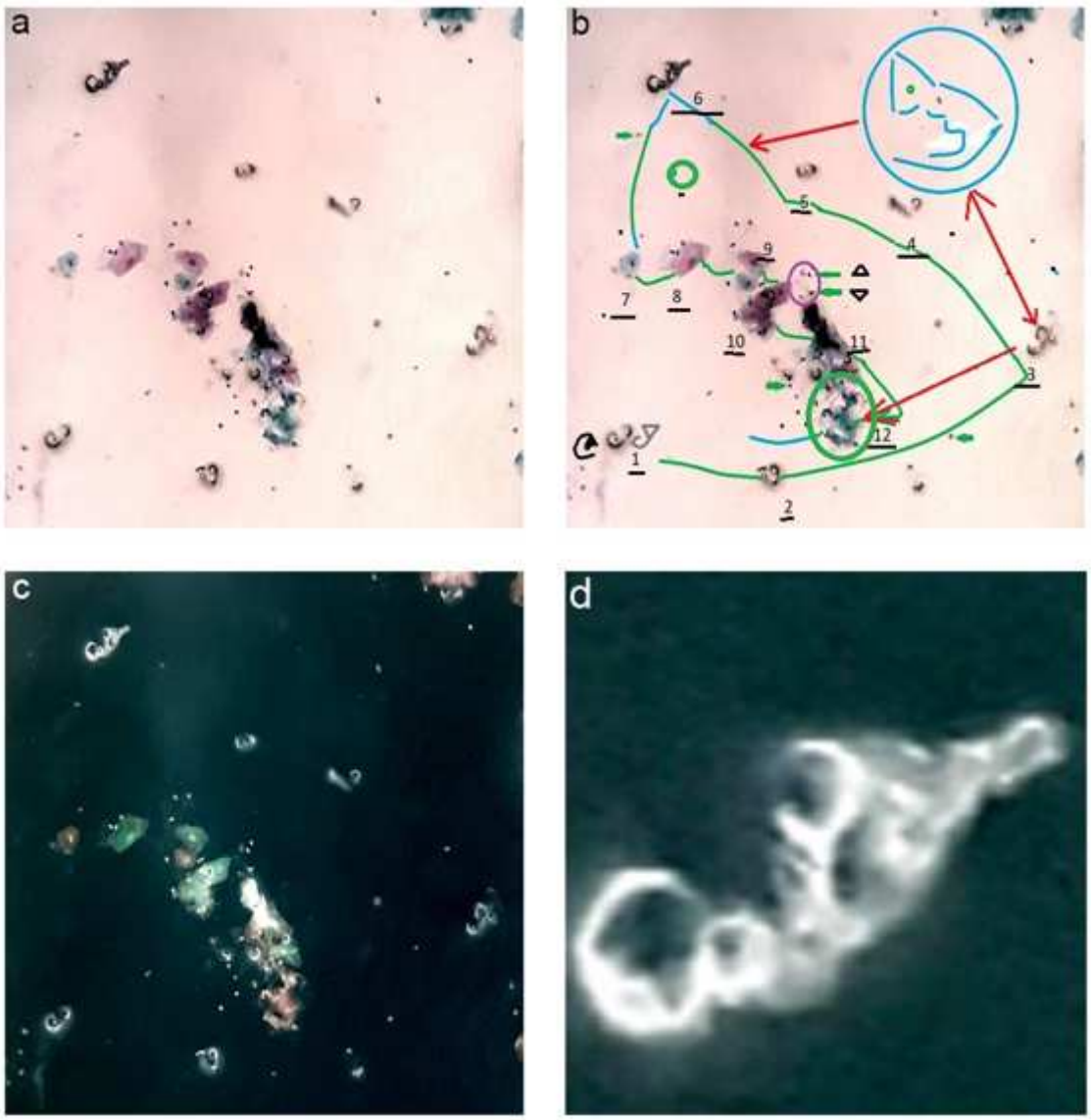


Figure 1

Clusters of malignant cells aligned in progressive order sequences with cell metamorphosis retrodifferentiation

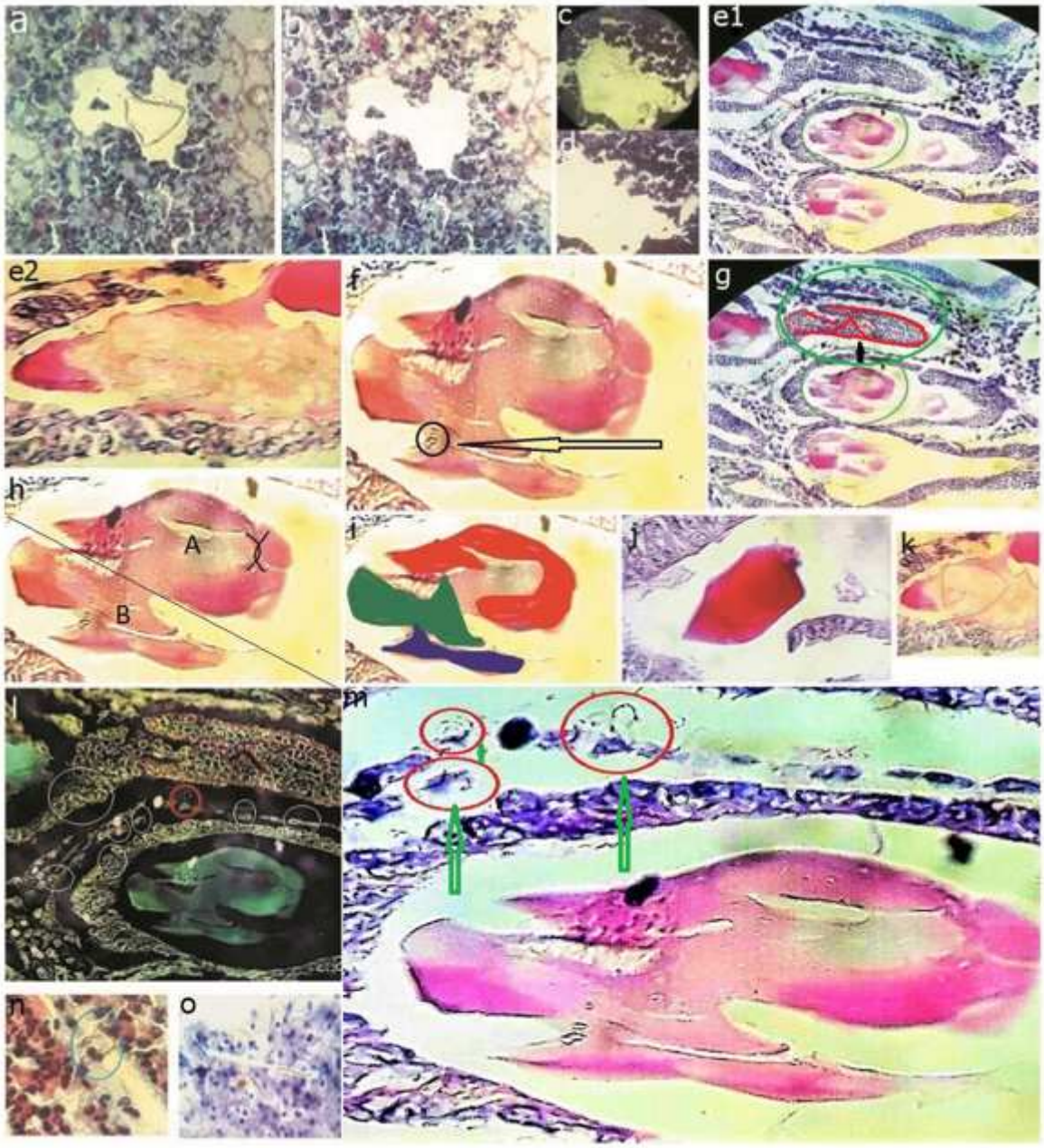


Figure 2

Tc represents the geometric triangular spiral cleavage precursor in the formation of these embryoblast entities . We can observe how the tumor epithelial cells around Tc indicated with a red circle, have acquired the Tc phenotype , therefore behaves at distance molecular communication.

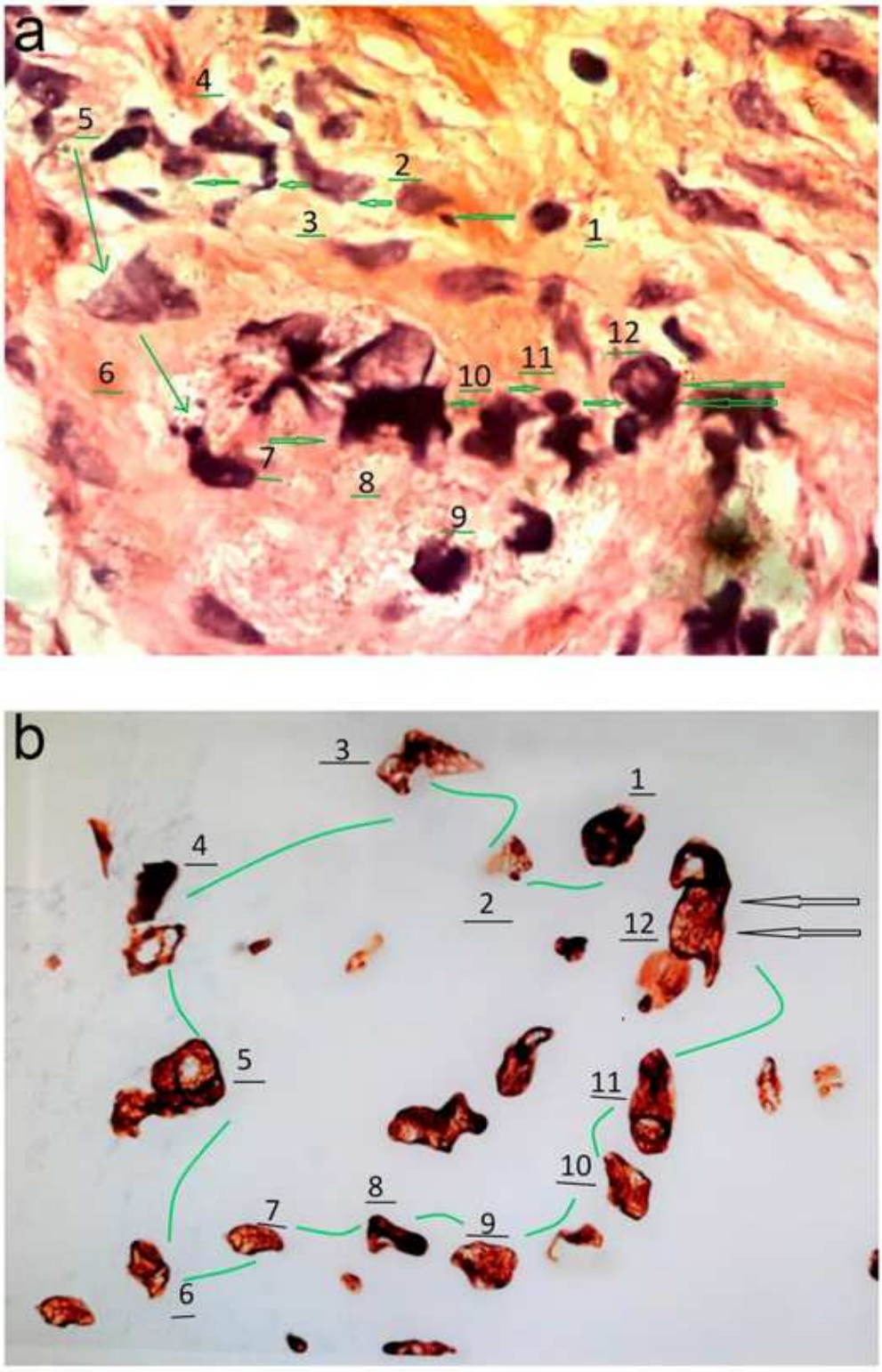


Figure 3

Clusters of malignant cells aligned in progressive order sequences therefore behaves at distance molecular communication , ending in the generation of an embryoblast entity

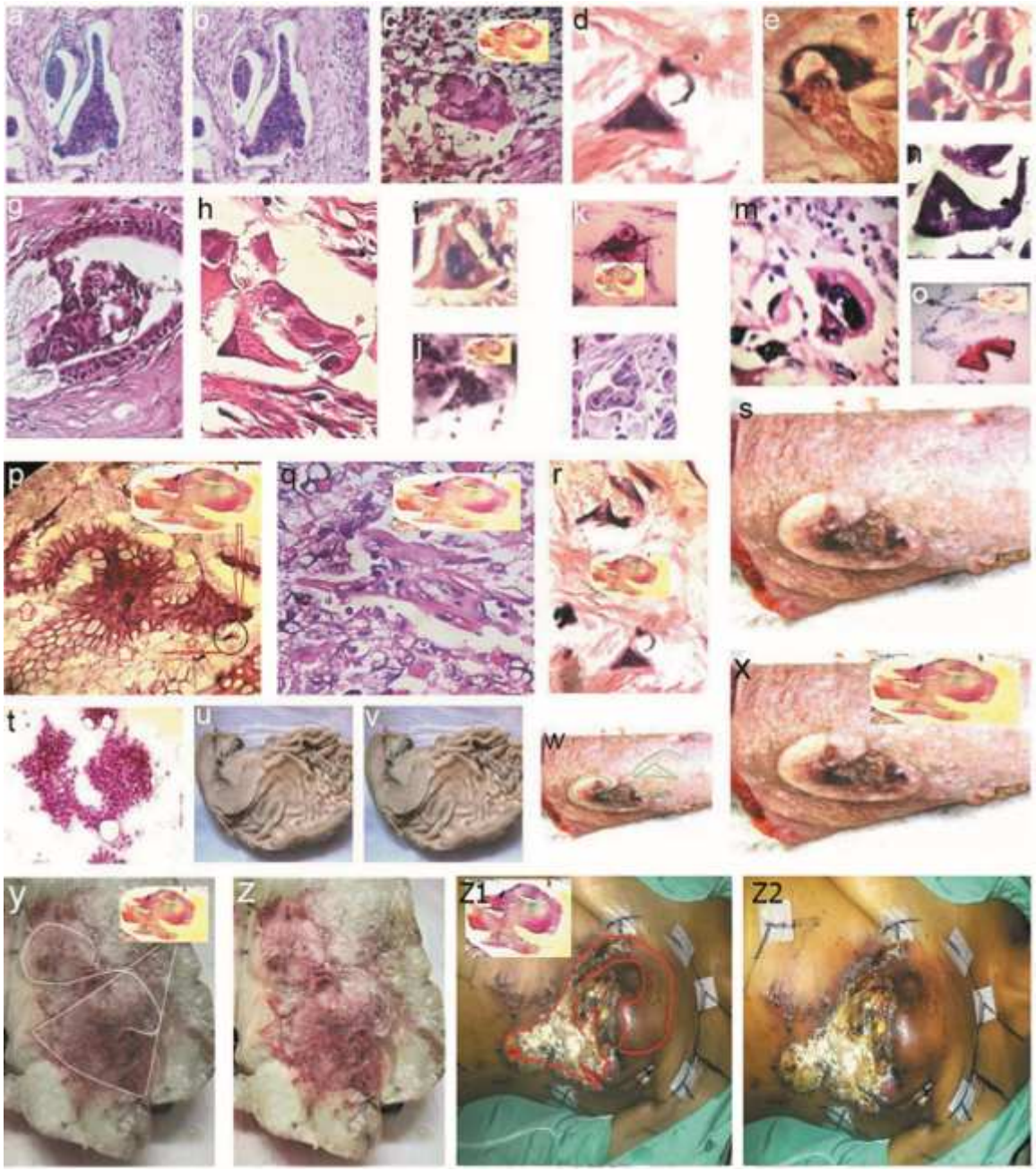


Figure 4

Transfer of information from Tc crystal protein to a group of tumor cells in different cancer scenarios Represents the "evolutionary cycle" stage 8 and 9, the sequence in which Tc transfers information to tumor cells or groups of cells in various scenarios, changing the phenotype of the tumor cells to the crystal phenotype of Tc a,b) breast cancer HE 40 X stain. c) prostate cancer HE 40X stain. d, e , f , g , h) breast cancer HE 40 X stain. i,j,k,l,m,n,o, lung cancer HE 40 X stain. p,q,r) colon cancer HE 40 X stain, s) macroscopic view skin cancer amputation .t, u,v) stomach cancer micro -macroscopic view . w x) macroscopic view skin cancer. y ,z) soft tissue sarcoma z1 z2) macroscopic view breast cancer.

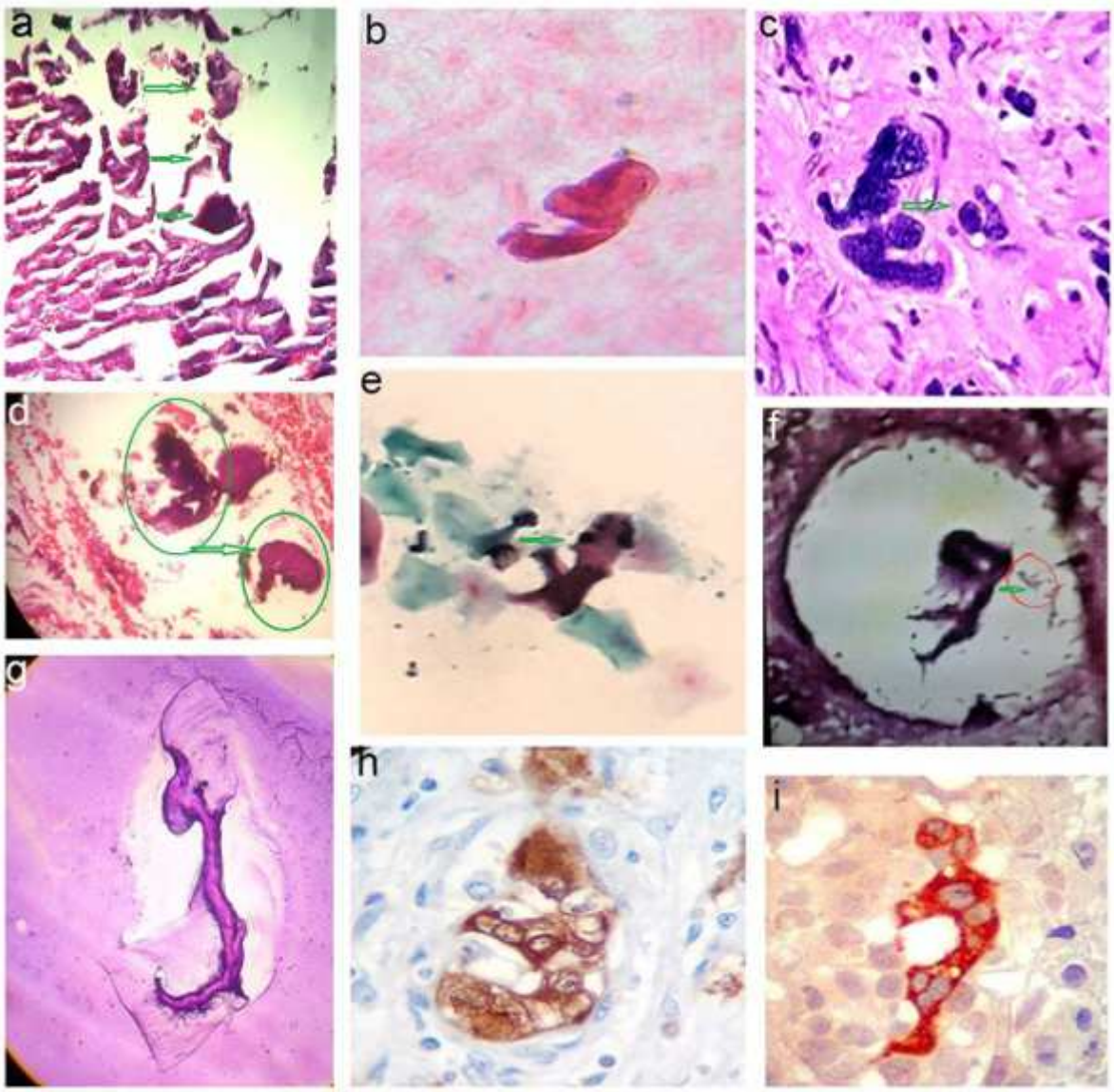


Figure 5

Evidence of cancer cell metamorphosis retrodifferentiation generating embryoblast like entities The hallmark of these entities is that its structure can exist in two visible chiral conformations and therefore behaves at distance molecular communication which results in clusters of malignant cells aligned in progressive order sequences (green arrows).

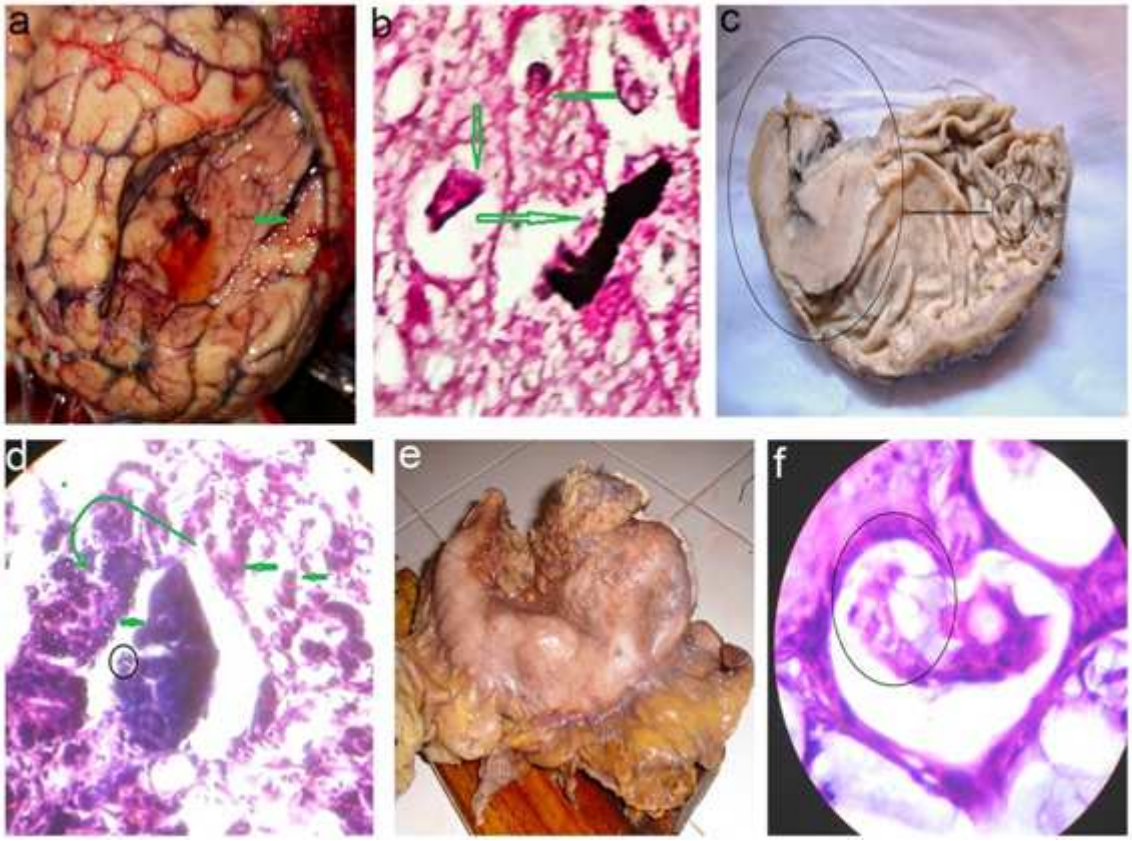


Figure 6

Glioblastoma multiforme l a) macroscopic phenotype lesion b) microscopic phenotype lesion, it can be seen how the two phenotypes are identical. Panel c,d) gastric cancer, the microscopic crystalloid phenotype is identical to the macroscopic tissue phenotype. Millions of copies of an individual microscopic crystalloid memory generate a collective macroscopic memory identical to the microscopic one in time (8 to 9 years) through the transfer of information, panel e,f) gastric cancer macroscopic phenotype identical to the microscopic phenotype

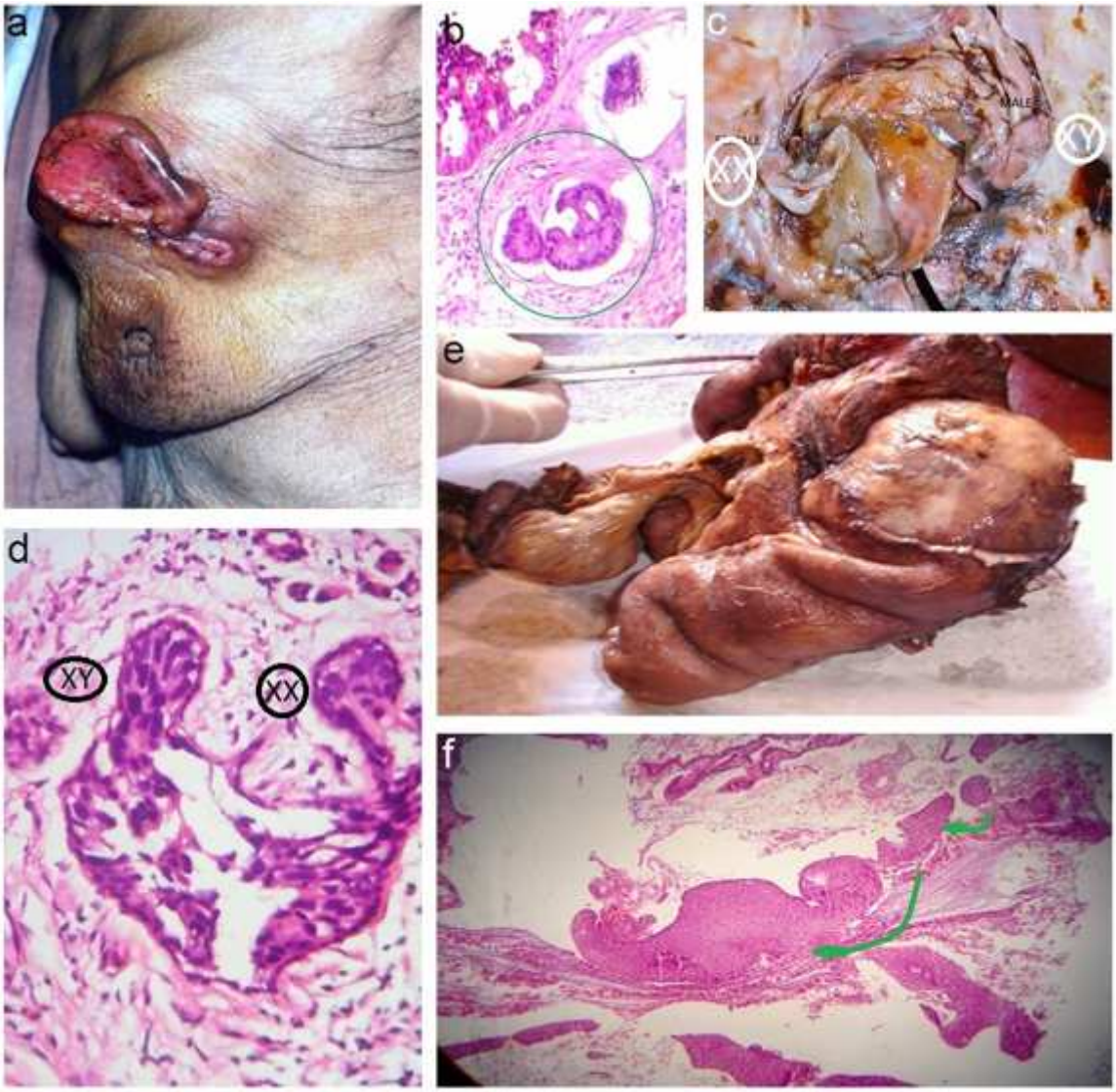


Figure 7

a, b . 80 year-old patient with a breast tumor. A giant breast tumor lesion can be seen that clearly shows an unusual morphology of cephalo-caudal pattern with an upper base and a lower base that is also triangular with a bilaminar caudal portion. The microscopic study of this lesion showed an identical lesion with a bilaminar component identical to the one observed macroscopically. The microscopic seed grew in time generating millions and millions of macroscopically identical fractal copies. c, This is a 50 year old tumor patient with a uterine leiomyosarcoma, panel c, a nest-like lesion where 2 triangular structures are seen in a mirror image in chiral position with a spiral component, 2 structures are seen with caudal-cephalic characteristics on the left in appearance embryoblast XX phenotype pattern due to the curvilinear morphology of its lines, on the right side is another less curvilinear morphology structure with XY phenotype pattern d) illustrates another microscopic embryoblast like entity with two visible chiral conformations : XY and XX phenotype patterns side to side. Material was captured in breast adenocarcinoma. H. E stain 40 x. e, f) Small intestine lymphoma, the microscopic phenotype iidentical to the macroscopic phenotype,

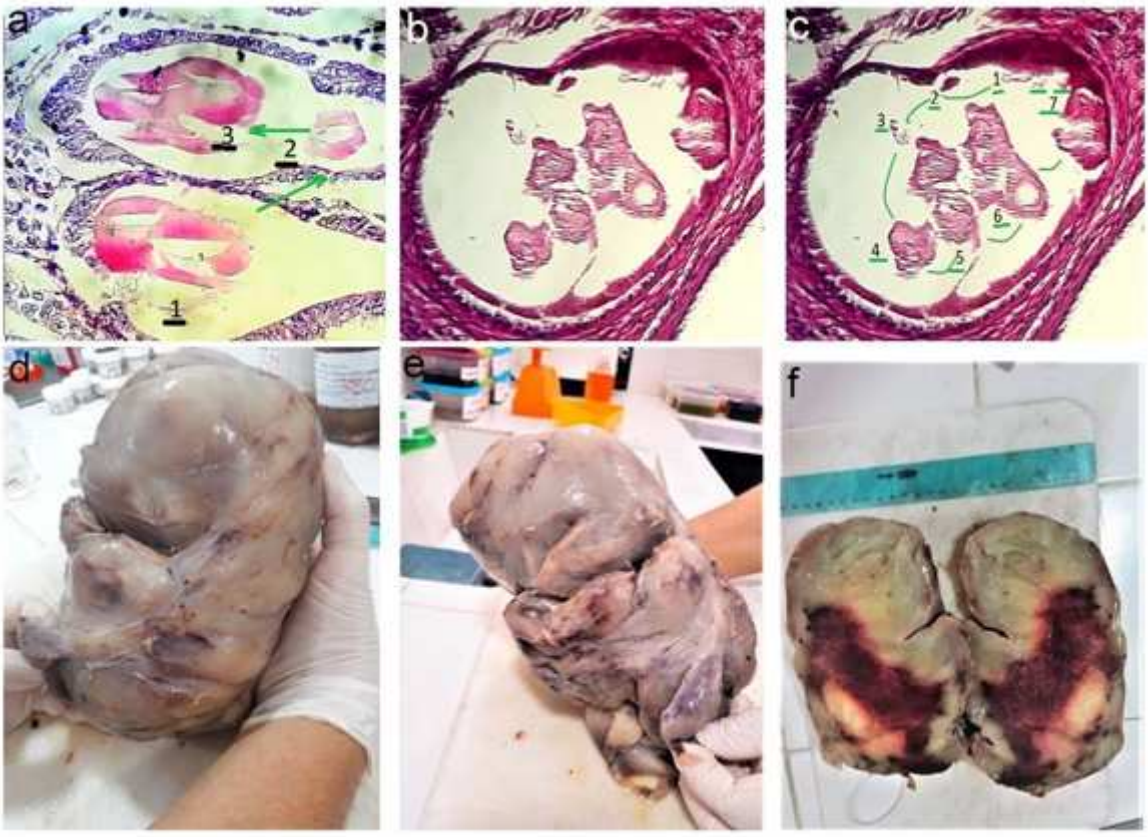


Figure 8

8a, b, c, d, e, f) This is a 35-year-old male patient with a retroperitoneal tumor lesion measuring 25 cm in length and weighing 2800 grams. Panels a, b, and c show the perfect tracing that we were able to carry out in this case. Panel a shows how the individual microscopic memory has its genesis inside a tumor gland from a molecular fluid that solidifies and crystallizes. Panel b,c irrefutably illustrates in stages 1,2,3,4,5,6,7 how the fluid secreted by the tumor epithelial cells solidifies and becomes crystalloid. From this individual crystalloid memory an easily discernible embryonic phenotype is sequentially formed in stages 3 to 7. Copies of this microscopic crystalloid memory generated an entity with clear fetal-type characteristics over a period of 8 to 9 years, identical to the crystalloid memory phenotype that served as the mold. Panel d,e, shows an almost perfect fetal macroscopic structure in profile and from the front, panel f shows a cross-section of the characteristics of the tumor that was diagnosed as a component of a sigmoid colon carcinoma.

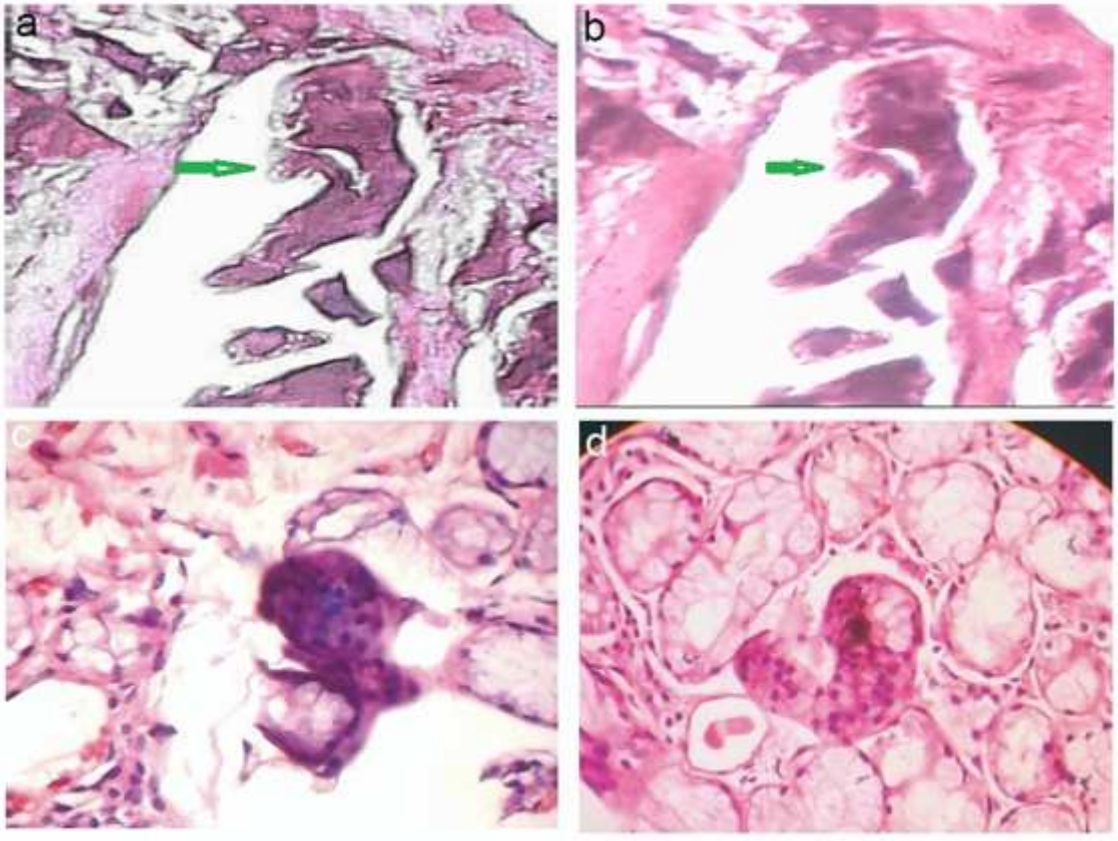


Figure 9

Evidence of cancer cell metamorphosis retrodifferentiation

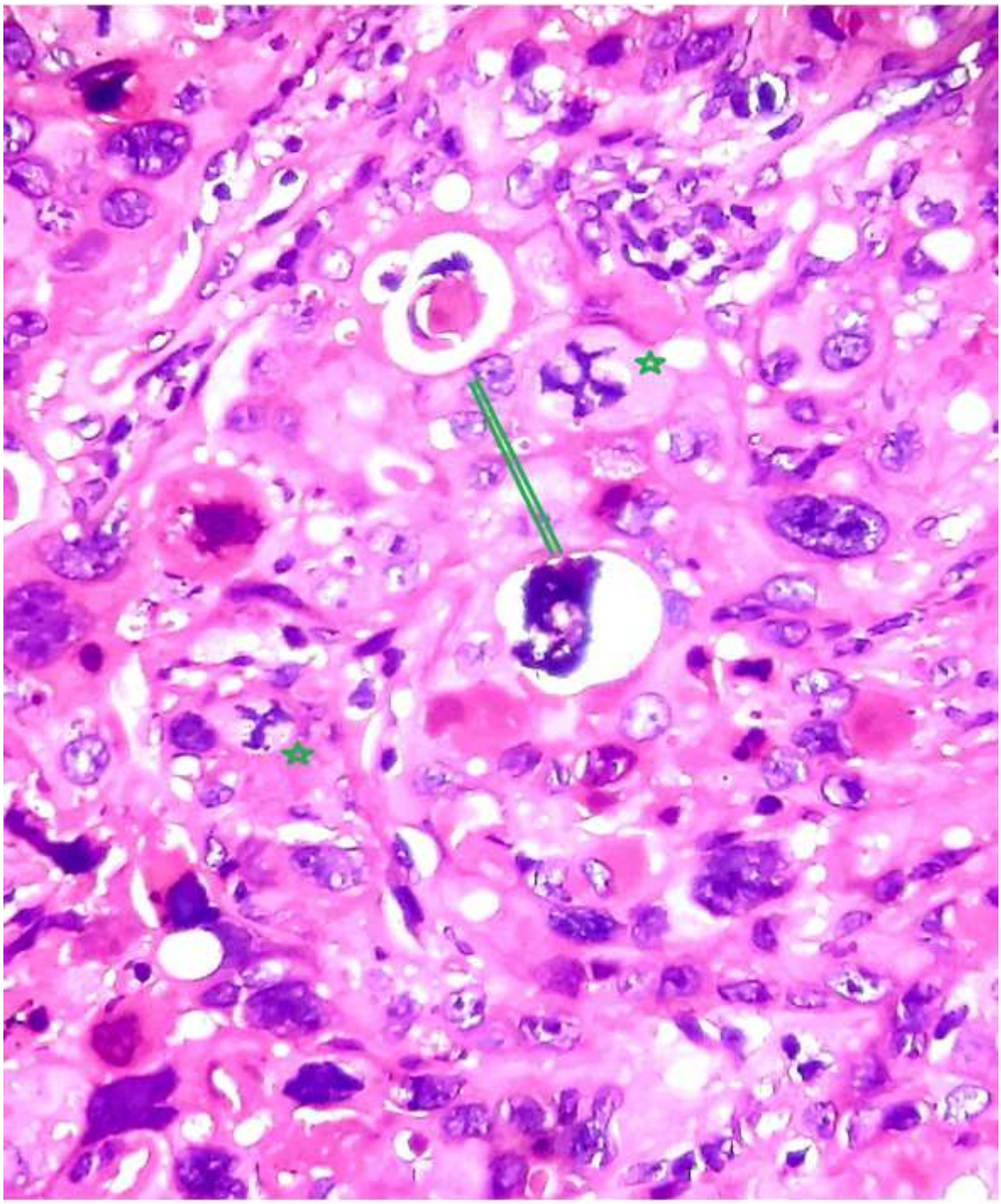


Figure 10

Image illustrates an aggressive squamous cell malignant tumor with great cellular pleomorphism and atypical mitosis*, in the middle of the field , arises an embryoblast-like structure with vestiges of incontrovertible upper and lower limbs , located within a blastocyst -like cavity with the registered hallmark of these entities: generating a mirror image. In tumor biology extreme disorder via cellular injury, mutations, viruses and cellular senescence generates via retrodifferentiation extreme biological order - embryoblast like entities.