Journal of Oncology Research and Therapy
Berlanga-Acosta J, et al. Oncol Res Ther 11: 10339.
www.doi.org/10.29011/2574-710X.10339
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Review Article

Peyton Rous Cells-free Filtrates: Significance to Validate Somatic Cells Memory Biological Impact

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Citation: Berlanga-Acosta J, Fernandez-Mayola M, García-Ojalvo A, Suárez-Alba J, Nasruddin NS, et al. (2026) Peyton Rous Cells-free Filtrates: Significance to Validate Somatic Cells Memory Biological Impact. J Oncol Res Ther 11: 10339. DOI: 10.29011/2574-710X.10339.

Received Date: 17 April, 2026; **Accepted:** 23 April, 2026; **Published Date:** 27 April, 2026.

Abstract

The controversial concept of somatic cellular memory emerged in the early sixties of last century. The pioneer studies by Coring and McConnell´s in planarians showed that this flatworm´s cells "learn", and transmit the experiences to regenerating descendants once their body was fragmented. Cellular memory concept has expanded following the demonstration of topographic memory in fibroblasts, respiratory, muscle, and skin cells under physiological and pathological processes. The discovery and molecular validation of the epidemiological evidence of a metabolic memory in diabetics' cells, inaugurated a new era in which an epigenetic program dictates the clinical phenotype of diabetes complications and other non-communicable diseases. The emerging evidences on personality changes in organs transplant recipients by the suspected horizontal transference of unidentified drivers, has nurtured the interest in somatic cells memory and epigenetics. In line with this putative horizontal transference of cellular memory codes, we discuss here a chronologic sequence of studies conducted by our group, in which we reproducibly demonstrated the recapitulation of histopathological pathognomonic hallmarks of diabetes, arteriosclerosis, and cancer; in rats, nude mice, and zebrafish as recipients of human cell-free filtrates, elaborated from pathologic tissues of subjects affected by these three conditions. The histopathologic changes appeared in a relatively short period of time, whereas the human "disease drivers" proved to override interspecies biological barriers. We deem that an epigenetic program is the propeller for what we dubbed as pathologic cellular memory. The identification, mechanistic validation, and ultimate antagonization of these pathologic memory drivers, may open novel therapeutic opportunities for non-communicable diseases.

Keywords: Somatic Cells Memory; Non-Synaptic Memory; Epigenetics; Metabolic Memory; Non-Communicable Diseases.

Introduction

The enlightening review by Flores and Liester on cellular memory [1], sparked the inspiration to retrace the lanes transited before. It also encouraged us to update and nurture with recent findings the notion we raised years ago, about the passive transmissibility of cellular memory, and how this memory imposed the donor´s message, driving to the recapitulation of its histological markers in the tissues of the recipient animals.

The fundamentals of cellular memory seem to be conceptually established in the early sixties [2] when Coring and McConnell announced that planarians are able to learn a task and transmit these experiences to regenerating descendants following decapitation [3, 4]. These were the leading findings to propose that the ability to remember by encoding and storing information, was not privative of nervous cells-mediated synapses. Cellular memory, although controversial [5, 6] is mostly acknowledged as an ancestral and evolutionarily conserved ability used by cells to "learn and recall" the experience of a primary insult, and assist in rapid cellular adaptation and survival if the same stressor subsequently appears [7]. In other words, cellular memory also known as somatic memory, describes the ability of cells to remember. Observations in organisms that lack a nervous system, such as bacteria, fungi, and plants, also support the existence of a somatic, non-synaptic memory [1, 8]. The process of embryo stem cells lifetime differentiation [9] and the ability of immune cells to recognize, remember, and rapidly respond to a previously encountered repertoire of antigenic challenges, are perhaps the most illustrative examples of non-neuronal cellular memory in vertebrate organisms [10]. The metazoan´s evolution has conserved the multiprotein Polycomb complex as an essential actor in maintaining the cellular program of differentiation memory [11]. Thus, Polycomb acts a major cellular identity memory guardian by controlling transcription and editing an irreversible epigenetic code [11]. The constellation of cellular memory evidences has progressively expanded during the last few years: (1) fibroblasts' topographic differentiation memory [12, 13], (2) muscle cells mass memory [14], (3) skin inflammation memory [15], and (4) respiratory allergy inflammatory memory [16].

The emerging evidences on personality changes in those heart and other parenchymal organs transplant recipients, mirroring the personality traits of their donors have surpassed the limits of what is imaginable and expected. About 89% of all transplant patients experience personality changes following organ transplantation, regardless of which organ was received. These changes include what in donors´ life were preferences for food, music, art, sex, recreation, and career, as well as names and sensory experiences. In line with these observations, others describe changes in the mood, behaviour, and memories in blood transfusion recipients after receiving blood from another person [17]. While determining the driving factors behind the personality changes following organ transplantation may be miles ahead, the existing evidences indicate that cellular memories are transferred from donor-to-recipient via the transplanted organ [18], whereas the organ´s recipient subject, replays events of the donor´s life. In analogy to the above-described scenario, we have accrued experimental evidences in which otherwise normal animals reproduce archetypical histopathologic markers of diabetes, cancer, and peripheral arterial disease, through the administration of a cells-free filtrate (CFF) prepared from "diseased tissues" of humans affected by these conditions [19]. It advised that these CFF contain transmissible, soluble messages that succeed in imposing and recapitulating the pathologic donors tissue phenotype. Although a variety of cell structures are hypothesized to participate in information storing we put forward the hypothesis that these fascinating events are mostly driven by epigenetic mechanisms in which epigenetic messages, for instance, non-coding RNA may be transferred to a novel host organism, consequently priming the recipient´s cells to recapitulate the donor´s phenotypic or behavioural attributes [19]. Here we describe and discuss the chain of findings and the line of reasoning behind these studies. This sequence of studies progressively expanded from the initial diabetic metabolic/epigenetic memory to the concept of a hypothetical cellular pathologic memory in non-communicable diseases (Figure 1).

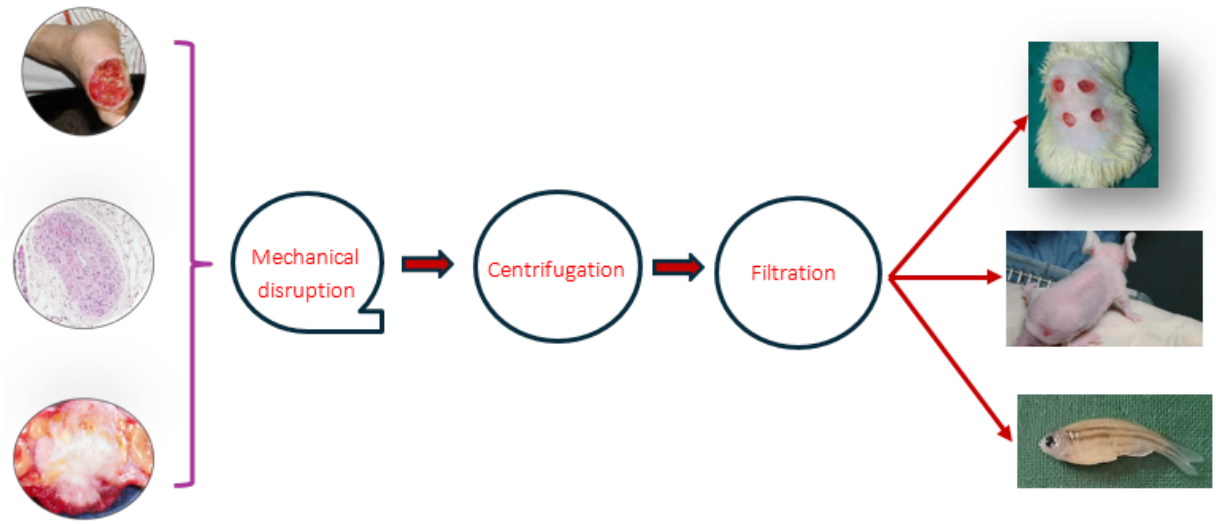

Figure 1: Road map from tissue sample to cell-free filtrate. Surgical tissue samples included granulation tissue from foot ulcers, as arteries, and nerves from diabetic subjects. In subsequent studies the samples were based on CFF derived from pathologic arteries from critical limb ischemia in non-diabetic patients. Thirdly, we began to study different malignant tumors after histological grading. Samples were mechanically disrupted in a TissueLyser with normal saline as vehicle with no other additive, centrifuged, and 0,2µm-filtered. Recipient animals were rats with dorsal full-thickness wounds, nude mice, and juvenile zebrafish. Protein concentration was our reference value for the administrations.

Brief concepts of epigenetics

The early discoveries on the molecular mechanisms of cell differentiation and development, and the subsequent identification of epigenetic drivers behind diabetes and cancer, has progressively propelled epigenetics to evolve from a collection of diverse phenomena to a defined and far-reaching field of Biology [20]. Epigenetics, in a broad sense, represents the bridge between genotype and phenotype-a phenomenon that changes the final outcome of a coding gene without altering its underlying DNA sequence [21]. The most illustrative example of what epigenetic tools may achieve, is the broad diversity of cell types with disparate, yet stable profiles of gene expression and distinct functions, all emerging from a zygote with an identical genotype [22]. Thus, this developmental process of destiny specification and phenotypic and functional differentiation may be considered an epigenetic phenomenon, in which each cell is endowed with a specific epigenetic landscape [23, 24].

Epigenetic mechanisms are highly regulated by proteins that establish, read, and erase specific modifications, thereby defining where and when the transcriptional machinery can access the primary DNA sequences to conduct a biological event [25]. In other words, epigenetics refers to a set of self-perpetuating, post-translational modifications of DNA and nuclear proteins that produce lasting alterations in chromatin structure as a direct consequence [26]. While some epigenetic marks are stable over time in particular tissues, others demonstrate developmental plasticity. Environmental factors such as maternal starvation, parental stressful experiences, and blood glucose levels for example, have been demonstrated to impact the epigenome of adult and embryo cells [27-30]. Some of the epigenetic alterations associated with maternal starvation in fetal life persist through to adulthood, likely contributing to late-onset cardiovascular disorders and type 2 diabetes [27]. Increasing evidences indicate that non-DNA sequence-based epigenetic information, can be inherited across several generations in organisms ranging from yeast, plants, and humans [31]. Interestingly, this epigenetic code-derived events are operated through three major processes: DNA/RNA methylation, post-translational modifications of histone proteins, and non-coding RNA modifications [32, 33]. The long-time preservation of a certain epigenetic signature translates in the cellular ability to retain phenotypic and behavioural traits, typical of the donor organism from which they originated. This concept explains for instance, why cultured cells from a diabetic subject, irrespective to the number of culture passages and ideal environmental conditions, preserve representative qualities of the donors' pathology. This is plainly illustrated with diabetics' fibroblasts and endothelial cells [34].

Chronic non-communicable diseases

Diabetes, arteriosclerosis, and cancer are among the most prevalent chronic non- communicable diseases (NCD), representing leading causes of global morbidity and mortality [35]. Epigenetic studies focusing on diabetes, arteriosclerosis, and cancer; reveal the crucial role of abnormal epigenetic programs that endure what we call as "pathologic cellular memory", implicated in the onset of a clinical phenotype, disease complications progression, and an individual's clinical course [36]. Accordingly, changes in DNA methylation and chromatin remodelling appear as major epigenetic operators involved in the pathogenesis and onset of these diseases, implicating also stem cells compartments [37].

1- Diabetic metabolic memory (DMM): The foundational lesson

DMM is an alluring biological and epidemiological concept that emerged from observations of the 1983 and the 1990´s diabetes and its complications control clinical trials. These studies highlighted the pathophysiological significance of early glycemic control, as the major mediator of the development and progression of diabetes complications. Thus, the concept in essence states that despite achieving a tight glycemic control, the organism continues to exhibit various inflammatory responses and complications associated to early hyperglycaemic spikes [38]. This fascinating phenomenon delineated for the first time a connection between irreversible and progressive disease complications, with the ability of non-neuronal cells to "remember" a primary insulting stress, that for this case is blood glucose level [38-40]. Unquestionably, diabetes became the pioneer and most convincing scenario on how an exogenous factor like glucose, is able to engrave an epigenetic pathologic memory that restlessly steers the path of the disease [41, 42]. The arduous decoding of DMM developed by Assam El-Ossta rendered the prime and landmarking evidences on how uncontrolled glycemic spikes impacted the cellular core of the epigenetic machinery, establishing the molecular bases of a protracted inflammation and oxidative stress [43]. During our studies of diabetic chronic wounds, we observed that diabetic granulation tissue arterioles somehow "inherit" and recapitulate in a period of a few days, a collection of histopathological features of chronic evolution that typically characterize diabetic microangiopathy [44]. We consequently speculated about the existence of an aberrant angiogenesis program in diabetes, possibly geared by epigenetic drivers, and that ultimately lined up within the conceptual frame of epigenetic/metabolic memory [45, 46]. In order to examine this hypothesis, we leveraged from the centennial experience of classic Peyton Rous´ cell-free filtrates of tissue homogenates, which ultimately contain the whole spectrum of cellular messages. These initial studies encompassed the administration of CFF prepared with granulation tissue, popliteal artery, and peroneal nerve surgical samples—all derived from lower extremity amputations. Cosmetic mammoplasty tissue from healthy donors acted as controls of the human-to-rat xenotransplant. A set of experiments were gradually conducted in which rats with round full-thickness wounds were intralesionally infiltrated with CFF prepared from the above-mentioned samples. Within seven days of wounds' exposure to diabetic homogenates, typical histopathological changes of microangiopathy (Figure 2) and neuropathy were generated on the background of healthy recipient rats [47]. In essence, the arterioles of the wounds mirrored the collection of arterial histopathological changes detected in the soft peripheral tissues of the diabetics' lower limbs. Considering the crucial pathogenic relevance of advanced glycation end-products (AGE) from inflammation, oxidative stress to irreversible diabetic complications, and vascular remodelling [48]; we introduced an additional reference control group to interrogate about the capacity of glycated bovine serum albumin (BSA) to trigger arterial thickening or any other abnormal change. Glycated BSA perturbed the healing trajectory, promoted inflammation, but no arteriolar thickening was observed despite the high concentration of AGE (683.8 ng/mg). We, therefore, raised the notion that factor(s) other than acute glucotoxic reactants operate behind the observed vascular remodelling. Immunohistochemistry experiments showed that the recipient animal's granulation tissue cells mirrored the immunoexpression phenotypic pattern of the donor for all the pathogenically relevant markers studied [47]. Globally speaking, the type 2 diabetes experiments showed that CFF of granulation tissue and internal structures as arteries and nerves of diabetic subjects, contain unidentified signalers that beyond glucotoxic factors, prime the acute onset of arteriolar thickening, abnormal angiogenesis, and nerves damages.

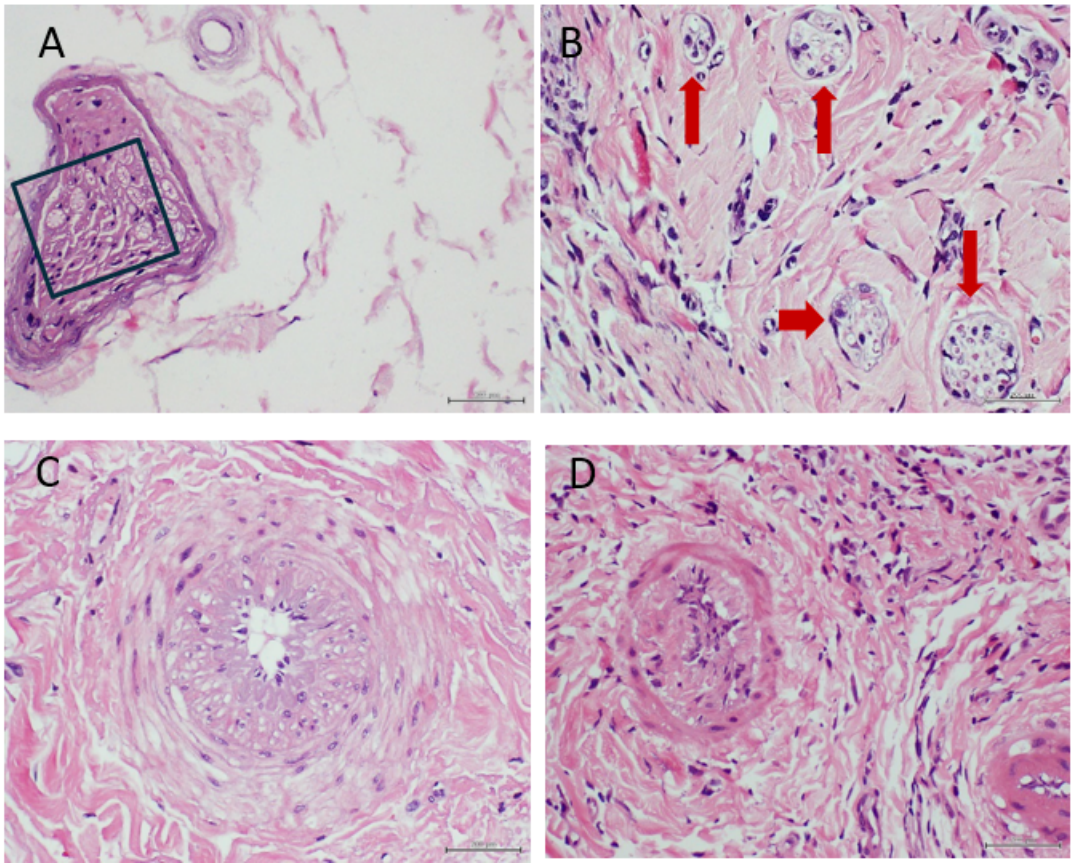

Figure 2: Recapitulation of pathognomonic histopathological markers of the donor patient in non-diabetic recipient rats. A: Representative cross-sectional image of a nerve fiber illustrating its cavitated appearance during Wallerian degeneration. Lysis and collapse of neurofibers are evident (inset). Histological section of skin from a lower limb in a diabetic patient. B: Histological section of skin border adjacent to the injection site in a rat treated with CFF obtained from tissues of a diabetic patient. Note the axonal degeneration process caused by neurofiber lysis, giving the axon a cavitated or cribriform appearance (arrows). C: Histological image of an arteriole from the skin of a lower limb in a diabetic patient. Representative image of diabetic microangiopathy, highlighting the concentric thickening of the media and a thickened and obliterating neointima. D: Representative of skin arteriole treated with cell-free filtrate generated from diabetic patient tissue. Note the marked thickening of a cellular and obliterating neointima. There is fusion of the media layer with the intima and intense perivascular collagen accumulation. H&E stain, 5 µm sections. 10x magnification. Scale bar 200 µm.

2- Histopathological markers of human peripheral arteriosclerosis are recapitulated in rats: A serendipitous finding

Some of the latest experiments conducted with diabetic tissues-derived CFF included groups of rats administered with CFF obtained from non-diabetic, peripheral arterial disease/critical limb ischemia patients. At that point we conceived these groups as one of the concurrent controls in which we expected nothing relevant to be found, given the glucocentric foundation of the diabetic metabolic/epigenetic memory. However, and against every prognostic, these and subsequent formal studies focusing on the effect of non-diabetic arteriosclerotic vessels, showed that 7-days of administration with the non-diabetic arteriosclerotic-derived filtrate, induced the recapitulation of angiogenic and arterial anomalies within the recipient rat-granulation tissue. Interestingly, these rats reproduced the donor's occlusion pattern characterized by the projection and luminal encroachment of collagen bundles and the presence of fusiform, fibroblast-like cells, apparently replacing endothelial cells. This event may represent an endothelial-to- mesenchyme reprogramming process (Figure 3) [49]. The so-called "aberrant angiogenesis" was also observed, in which muscle myofibrils are replaced by vascular- like channels

that may contain an endothelial collar, so that one tissue lineage is replaced by an unrelated one [50]. Furthermore, as described for the diabetes study, immunohistochemistry experiments confirmed that the arteriosclerotic material recipient rats, entirely recreated the immunoexpression pattern of vascular critical markers found in the pathologic donor samples [49]. These enticing findings meant a turning point in our early hypothetical conception. It was clear that the passive transference of diseased human tissue messengers, and the subsequent reproduction of the donor´s histopathology in healthy animals' organs, was not circumscribed to diabetes and therefore there was something beyond the metabolic memory. This fact led us to interrogate what could be the experimental outcome when CFF were prepared from another non-communicable disease.

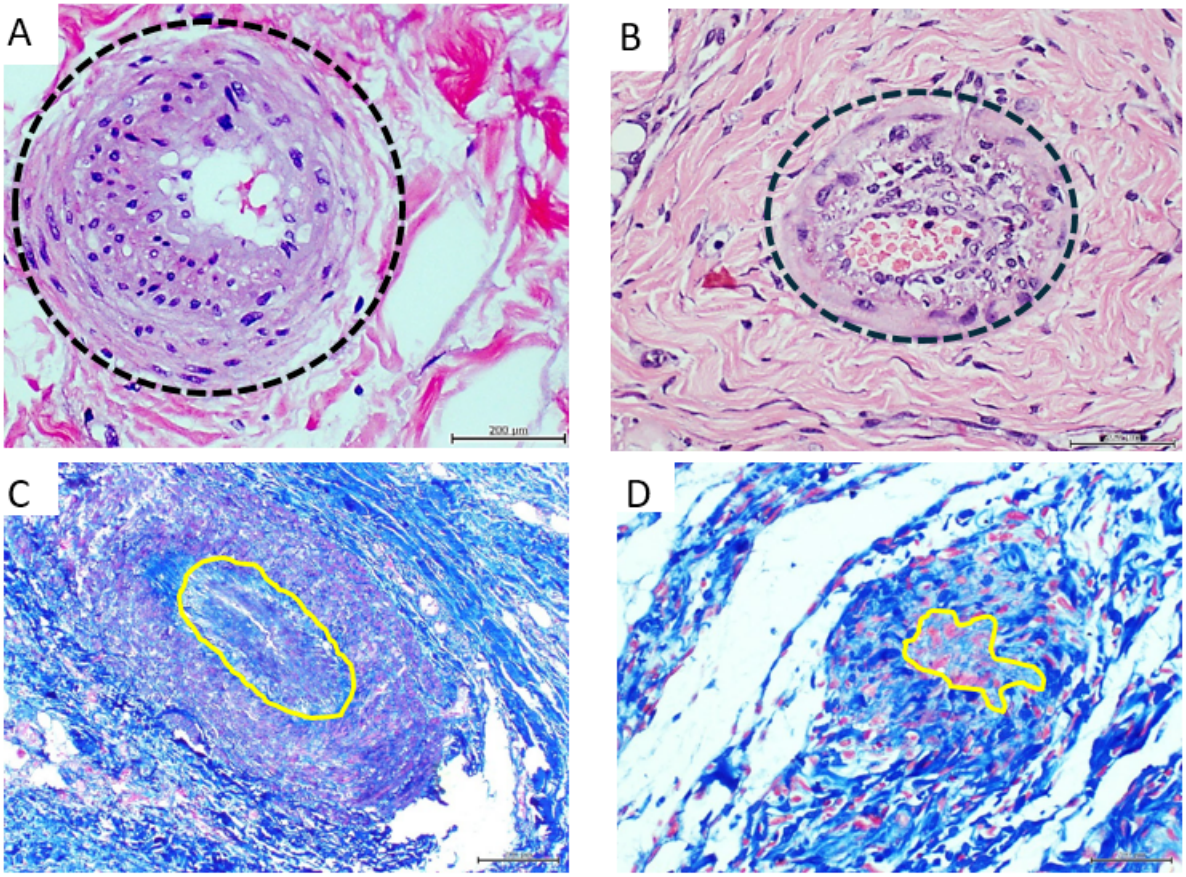

Figure 3: Rats' arteriolar remodelling after exposure to non-diabetic arteriosclerotic arterial tissue CFF. (A) Human donor arteriole with an active process of intimal hyperplasia, subendothelial infiltration, luminal narrowing and concentric expansion of the media layer with basophilic nuclei. (B) Vascular response to human arteriosclerotic CFF in which a rat arteriole exhibits wall thickening, abnormal subendothelial cellular infiltration, and disorganization. The lumen is becoming obliterated. (C) Human donor arteriole showing degenerative wall changes including collagen induration within the walls and lumen (yellow lines) as judged by blue staining of the Mallory reaction. (D) Rat's arteriole with incipient luminal invasion by protruding collagen material encroaching the lumen (yellow lines). The lumen appears occluded. All 5-µm sections, H/E and Mallory trichrome staining. Magnification x 40. Scale bar: 200 µm.

3- Human tumors-derived CFF induce premalignant and malignant lesions in mice and fishes

Having reformulated the initial idea on metabolic memory after the lessons learned from the non-diabetic arteriosclerotic study, we selected cancer as a third non-communicable condition. Accordingly, we examined what the outcomes would be after exposing healthy animals to CFF prepared from human malignant tumors. To test the hypothesis of a putative pathologic cellular memory a first study was initiated using: (1)- CFF elaborated from samples of mammary invasive ductal carcinomas (IDC) of high histological

grade, (2)- A locally invasive pleomorphic sarcoma that invaded the right hemithorax of the patient. The subcutaneous administration to BALB/c-Foxn1nu/Cenp nude mice of increasing protein concentrations of IDC homogenates for 6 and 12 weeks, induced lungs atypical adenomatous hyperplasia, foci of lepidic and solid growth poorly-differentiated adenocarcinomas at the two time points (not shown). The sarcoma CFF administrations for 30 days triggered proliferative changes including: lung adenocarcinomas, a subcutaneous, poorly-differentiated mesenchymal cells tumor, a lymphoadenoma, and multiple gastrointestinal adenomas. Furthermore, suspension of sarcoma CFF administration after a month of daily treatment in a group of mice, did not attenuate the ongoing carcinogenic process. Contrarywise, tumors progressed (Figure 4) and impacted in animals' health, suggesting that authentic neoplasms were established since their early time point, and that these lesions had presumptively accumulated sufficient "self-capabilities" for an autonomous progression, which meets with one of the classic cancer hallmarks [51]. Taken together these findings indicate that tumor crude homogenates contain soluble transforming codes, that in a short period of time disrupt tissues' proliferative and differentiation programs leading to progressive neoplasms.

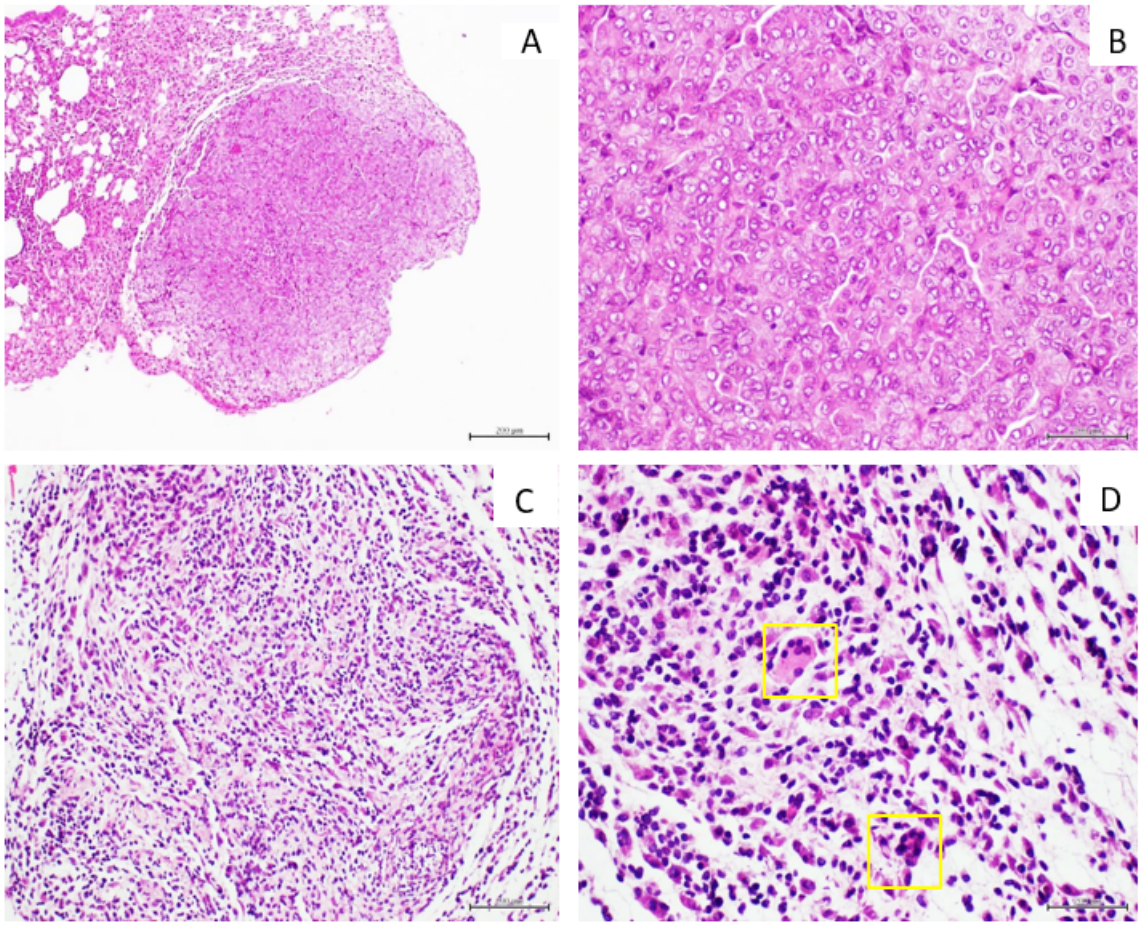

Figure 4: Sarcoma CFF induced epithelial and mesenchymal tumors. A- low power image (x 4) of a lung tumor in a mouse treated for a month with the sarcoma CFF. B- shows the typical histological aspect of a lung solid adenocarcinoma (x 20). C- low power image (x 4) of a solid nodule found during autopsy within the interscapular fat tissue. D- this tumor exhibited poorly-differentiated fusiform, spindle-like, round basophilic, and multinucleated cells (yellow lines squares), being interpreted as a poorly differentiated mesenchymal tumor (x 20). All 5-µm sections, H/E staining. Scale bar 200µm.

In a subsequent study we broadened the spectrum of human malignant tumors CFF to be administered to nude mice groups, along with the corresponding controls derived from tissues of healthy donors undergoing cosmetic surgeries. The set of human malignancies included mammary ductal carcinoma, pancreatic adenocarcinoma, and melanoma. Again, all these tumors CFF proved to transform cells originating a diverse set of tumors in parenchymal internal organs in otherwise normal mice [52]. An additional experiment of this study pursued to learn whether the exposure of ZF embryos during the morphogenesis period, would lead to the overexpression of some cancer biomarker as mature protein. Accordingly, the incubation of ZF embryos with breast ductal carcinoma homogenates for approximately 60 hours, elicited the expression of c-Myc and HER-2 in a constellation of embryo cells as melanocytes, notochord, cephalic, and eye cells (Figure 5); as compared to matched control embryos incubated with normal tissues CFF [52].

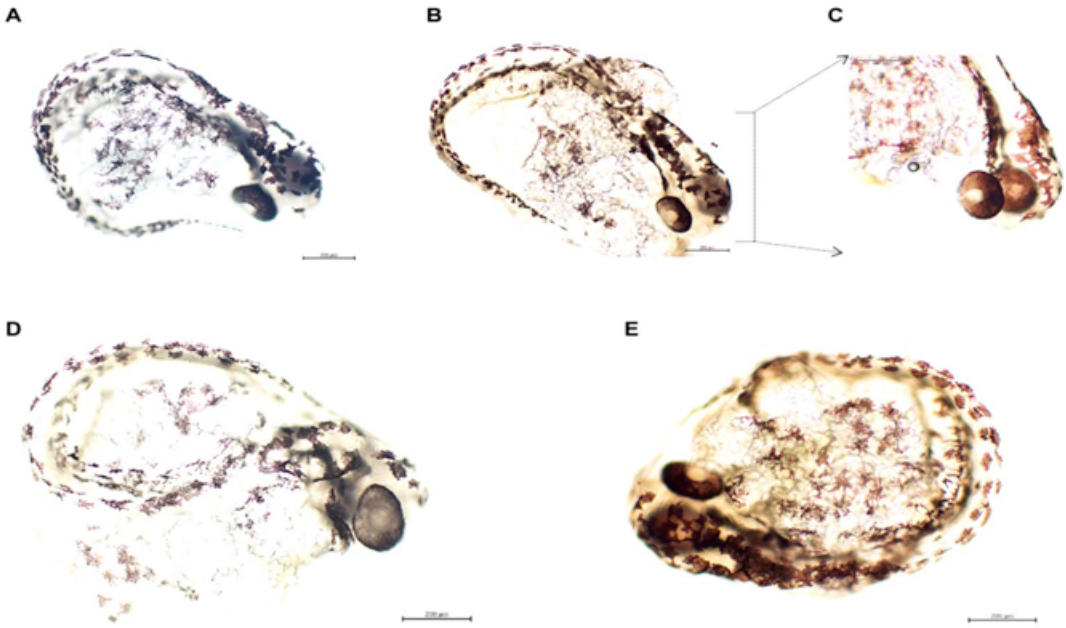

Figure 5: Expression of tumor markers by zebrafish embryos after incubation with malignant tissue-derived homogenates. (A) Embryo exposed to the healthy donor skin homogenate and incubated with an anti-c-Myc antibody. A light background is observed along the line of melanocytes upon the notochord. (B) Embryos exposed to breast ductal carcinoma homogenates. c-Myc expression by the same melanocytes' population and other cells of the cephalic pole was observed. (C) c-Myc expression by the eye cells and cells over the area of the rhombencephalon, cerebellum, and tegmentum. (D) Embryos treated with healthy donor-skin homogenates and incubated with an anti-HER-2 antibody. Again, melanocytes and cephalic pole cells exhibit a faint expression, which is in contrast with the remarkable expression detected in sample. (E) Corresponding to embryos exposed to breast ductal carcinoma homogenates. Melanocytes and notochord cells, alike cells on the cephalic pole over areas of the rhombencephalon, cerebellum, epiphysis, and optic tectum express HER-2. All magnification ×10, except C magnification x 20. Scale bar: 200 µm.

Finally, and continuing with ZF as an alternative animal model we examined whether the CFF of human malignant tumors would somehow modify cellular proliferation and differentiation patterns in a non-mammalian, aquatic organism. Hence, we injected for six weeks juvenile adult zebrafish with a CFF elaborated from an invasive pleomorphic sarcoma. Four weeks onward, the animals showed somatic deterioration, growing abdominal masses, and spinal deviation hindering swimming activity. The histopathological study disclosed that again, the sarcoma CFF originated premalignant and malignant changes (Figure 6) that included gastrointestinal stromal tumors, hepatocellular carcinomas, intrahepatic cholangiocarcinomas, and poorly differentiated tumors with cells of epithelioid aspect. Furthermore, multinodular foci of bile ducts hyperplasia with or without epithelial atypia, and Langerhans islets hyperplasia with nuclear atypia were also observed [53].

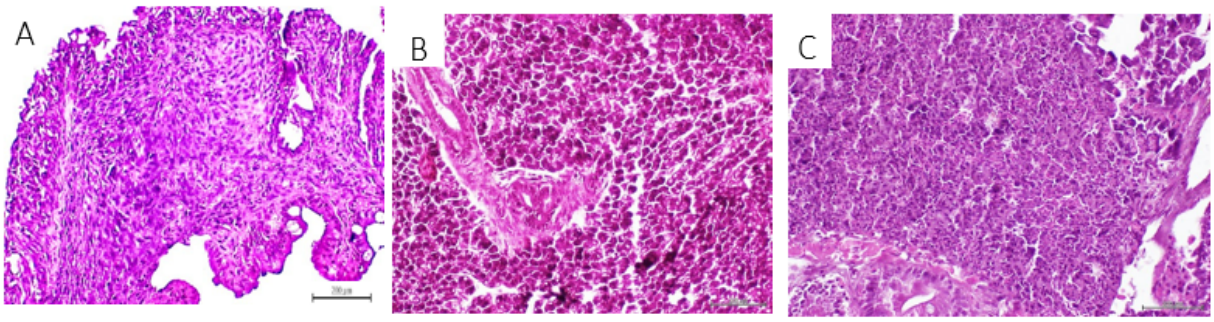

Figure 6: A-Intramural intestinal stroma tumor exhibiting a sarcoma-like aspect with abundant spindle cells. The nuclei appeared intensely basophilic, pleomorphic, atypic, and surrounded by a dense aspect-cytoplasm. B- Cellular discohesiveness, perinuclear vacuolation, areas of signet ring-like cells, hyperchromatic and atypic nuclei, and cellular pleomorphism are distinguished. C- Image of a poorly differentiated tumor of possible epithelial origin adjacent to the exocrine pancreas. Hypercellularity, architectural disorganization, cellular and nuclear pleomorphism are shown. All images correspond to 5-µm sections and H/E staining. Magnification X 40. Scale bar 200µm.

Discussion

In late 2012 we began to conceive the hypothesis that somatic cells harbor a disease code memory. As earlier mentioned, this hypothesis was inspired by two major observations of our group that may only be explained through the prism of an existing and transmissible epigenetic memory: (1) diabetic foot ulcers granulation tissue fibroblasts systematically cultured exhibited a molecular senescent program, deriving in reduced population doublings and replicative decay- despite successive passages in an optimal culture environment [54], (2) the histological landscape of diabetic microangiopathy is completely recapitulated by incipient and neo-formed vessels within a diabetic granulation tissue that is no older than two weeks [44], thus suggesting the existence of an underlying priming factor for the "acute inheritance" of the diabetic vascular disorders. These observations encouraged to interrogate if a free-of-cells diabetic tissue homogenate injected in otherwise healthy rats' wounds, would somehow replicate some pathognomonic phenotypic markers of the diseased tissue. Since the first study we learned that diabetic tissues host priming factors beyond glycoxidation products in both peripheral (granulation tissue) and internal structures (arteries and nerves), that are apparently uptaken by host animal cells, and that disrupt the wound angiogenic process reproducing the histology of microangiopathy in the scar tissue. This study, in addition to offer an unprecedented system to recreate histological features of diabetic limbs ulcers in a non-glucotoxic environment, incites to consider that diabetic tissues- derived circulating messengers, may systemically perpetuate organs damages in shorter periods of time than it is currently considered [55].

The second series of studies based in CFF obtained from non-diabetic subjects due to chronic limb ischemia, reproducibly demonstrated the reorchestration of the human donor's arteriosclerosis panorama in rats´ scar tissue arterioles. Of note again, the vascular remodelling events took place in a 7-days temporary window, whereas these arterioles recreated the donor´s fibroblast-like cells endoluminal invasion, the collagen encroachment and obliteration. All suggesting that these vascular memory factors may have driven a phenotypic/epigenetic reprogramming process [56]. Given that none of these changes were ever detected in the control animals, supports the authenticity of the findings, and excludes the possibility that these alterations are a mere pattern of endothelial immune-inflammatory reactivity to the human xenogeneic material.

Our third and fourth series of studies discussed here, demonstrated that human malignant tumors CFF may transform cells, inducing a histological variety of premalignant and malignant changes in mice and fishes. Accordingly, these studies suggest the existence, transmissibility, and uptake by host cells of caner signalers that impose a carcinogenic program in mature, fully differentiated populations of epithelial and mesenchymal cells. The legitimacy of the de novo formed tumors in host animals is supported by evidences of classic cancer hallmarks: (1) animals health deterioration, (2) histological evidences of lineal promotion–progression process, (3) tumors growth autonomy, (4) histological evidences of emboli of circulating atypical cells, (5) the malignant cells expressed tumors markers, and (6) the absence of a reactive, immunoinflammatory response associated with the human material inoculation [57-59].

Common to all these studies is the methodological procedure used so far. This is based on the elaboration of a crude, simple, cell-free filtrate derived from human pathologic tissue samples, with normal sterile saline solution as vehicle with no other chemical processing. This is the historical Peyton Rous´ methodology [60-61]. CFF may act as a vector of an extensive conglomerate of cell ingredients from proteins, exosomes to miRNA molecules. This view is supported by the presence of integral DNA, and RNA molecules, including miRNA in our samples of tumors CFF despite the mechanical processing of tissue disruption. After all, RNA molecules were successfully reverse-transcribed and amplifiable to DNA [62]. This fact turns conceivable the hypothesis that behind our observations, some kind of eukaryotic-to-eukaryotic horizontal transfer of a set of messengers as DNA and/or RNA, and metabolites may exist. For the particular example of cancer, it has been shown that oncosomes and oncometabolites may induce chromatin modifications, impinge on the epigenetic regulation of gene expression [63-65], and ultimately via this horizontal transfer, modify the functional phenotype of the recipient cells [66, 67]. Common to all these studies is the phenotypic recapitulation of the donor tissue histopathology in the target animal. Whichever are the drivers, they are able to override the natural interspecies barriers, irrespective of the recipient animal species (rat, mouse, or fish) and the nature of the donor´s pathological entity (diabetes, peripheral arterial disease, or cancer). Interestingly, another common factor is that tissue changes in the recipient animals are elicited in a very short temporary window, and with no major individual differences among the animals of a group. The briefness on the onset of these changes deserves further attention, considering that the arteriosclerotic remodelling and the multistage events of malignant transformation, are long-term evolution processes in humans [68]. Finally, there is also the observation that the morphological changes in the tissues of the recipient animals, are paralleled by the expression of proteins that represent authentic and pathognomonic biomarkers of the recapitulated condition pathophysiology. Again, these observations appear to challenge contemporary concepts of long latency period for the onset of morphological changes in non-communicable diseases [35]. Furthermore, we also deem that these human-derived signalers that enforce their pathologic code in the recipient animal species, would also challenge the concept of non-communicable disease for those processes in which a living pathogen is not pathogenically involved.

The notion on the existence and transference of a somatic cellular phenotypic memory has evolved from what seemed an unfounded suspicion [69], with the James V. McConnell´s controversial studies on planarian behavioral memory, to an ever-growing list of evidences including the perceived changes in recipients of red blood cells transfusions [17]. McConnell´s unbeatable major merit was to propose that "something outside the brain", which he anticipated to be RNA could be a possible factor for memory transfer [70]. In support to this clear foresight of an epigenetic ingredient in memory transference, stands the elegant evidence by Glanzman´s laboratory who showed the successful transference of a behavioural memory in a naïve recipient marine mollusk, implemented via RNA injection extracted from the nervous system of a sensitized counterpart. Hence, RNA seems to play a significant role in memory creation via epigenetic changes such as DNA methylation and acetylation [71]. Whether RNA is our missing link warrants further research. Conclusively, along these years we have witnessed that the Rous´s CFF elaborated from human pathologic tissue samples of three non-communicable diseases, contain and deliver donors´ disease codes, that enforce the recapitulation of specific and classic histopathological markers in normal animals, supporting our hypothesis on the existence of a transmissible “epigenetic cellular disease memory”. The ultimate selective manipulation of this keyboard, may entail future and promising therapeutic alternatives for the control of non-communicable diseases.

Author Contributions:

JB-A: Conceptualization and formal analysis, writing-review. MF-M, AG-O, JS-A, NSN, SF-P, YN-F, GP-F, DC-C: Experimental data generation, original draft preparation. EP-V and GG-N: project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: Funds derived from the account 3051-280 granted to Tissue Repair and Cytoprotection Research Group by BioCubaFarma Holding, Cuba.

Conflicts of Interest: The authors declare no conflict of interest.

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