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Hypothesis

Revisiting epithelial carcinogenesis

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Abstract

The origin of cancer remains one of the most important enigmas in modern biology. This paper presents a hypothesis for the origin of carcinomas in which cellular aging and inflammation enable the recovery of cellular plasticity that may ultimately result in cancer. The process is described as the result of dedifferentiation undergone by epithelial cells in hyperplasia due to replicative senescence towards a mesenchymal cell state with potential cancerous behavior. In support of the hypothesis, the molecular, cellular, and histopathological evidence was critically reviewed and reinterpreted when necessary to postulate a plausible generic model for the origin and progression of carcinomas. In addition, the implications of this theoretical framework for the current strategies of cancer treatment are discussed against recent evidence of the molecular events underlying the epigenetic switches involved in the resistance of breast carcinomas. Subsequently, is proposed an epigenetic landscape for their progression and a potential mechanism to restrain the degree of dedifferentiation and malignant behavior. Finally, is suggested a novel understanding of the involution and carcinogenesis of tissues associated with aging as a perspective that might inspire integrative approaches in the study and management of chronic diseases.

Keywords: Senescence, EMT, NF-κB, Inflammation, Epigenetics, Aging

Introduction

Cancer remains the second leading cause of death worldwide (1) despite the enormous amount of research and financial support devoted to finding a cure (2). In essence, is considered that the lack of understanding of cancer itself, and how it develops and progresses has prevented the development of effective therapeutic strategies (3, 4). The somatic mutation theory remains the prevailing paradigm and assumes that cancer is a genetic disease in which mostly alterations in the genetic material account for the cancerous phenotype (5). Therefore, the rationale has been to kill cancer cells usually by DNA poisons in combination with agents that target the molecular alterations associated with the aberrant genetic traits (6). Strikingly, most antineoplastic agents and radiotherapy induce cancer in humans (7) and the initial favorable response is temporal and followed by tumor progression despite the correct and complete administration of the protocols (8, 9).

The contribution of aging and inflammation to cancer development is mainly linked with mutations since the traditional view conveys that carcinogenesis is a multistep process related to genetic or chromatin damage (10). Altogether, the exponential rise of carcinoma incidence associated with age, especially in patients suffering from chronic inflammation (11) has been interpreted as the consequence of an increased likelihood to acquire defects in the genetic material of epithelial cells. Under this view, telomere attrition in aged cells and the production of oxidative stress by immune cells favor the attainment of malignant features by mutagenesis and chromosomal instability with the potential to evolve in cancerous behavior (12-14). Furthermore, the accumulation of senescent cells associated with aging is considered to contribute to

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structural and endocrine changes that may also promote the carcinogenesis of the affected tissues (15-17). In this regard, they produce cytokines, chemokines, growth factors, and proteases that attract and activate immune cells. In turn, the burden of inflammation and tissue disruption promotes cell proliferation and the epithelial to mesenchymal transition (EMT) (18, 19). The process of EMT has been linked with cancer invasion (20), metastasis (21), the generation of cells with features of mesenchymal stem cells (22) or cancer stem cells (19) that are drug-resistant (23), can evade the immune system (24) and may originate relapses (25). Overall, the conventional view suggests that in the first instance the entry to senescence prevents the progression of aged cells that possess genetic damage by arresting their cell cycles (26). However, due to defects in the normal clearance of senescent cells mediated by the immune system, they eventually accumulate and the combination of their paracrine and structural effects endorse carcinogenesis in the affected tissues (26).

The rationale of the somatic mutation theory is that genetic alterations provide a fitness advantage to the affected cancerous cells. Despite the sequence analyses of cancer samples identified over 4,000 missense driver mutations in 240 genes (27) new research has revealed an unexpectedly large number of mutations in normal tissues and a substantial fraction of the somatic mutations found in cancers are present even in the absence of neoplasia (28). In addition, the current paradigm is also challenged by several inconsistencies, for example, most oncogenes are essential players in the normal biology of cells (29), many carcinogens lack mutagenic effects (4), cancer cells show morphological and transcriptional convergence regardless of the initial cellular phenotype (30), and the cancerous behavior can be acquired by events of transdifferentiation (31). Moreover, is possible to revert the malignant phenotype by the induction of differentiation using chemical agents (32), vitamins (33), transcription factors (34), or interactions with the extracellular matrix (ECM) and the stroma (35).

The limitations of the prevailing model to explain the plasticity and convergence of the cancer cell have inspired novel proposals. For example, cancer is now increasingly conceived as a disease initiated by genomic instability that allows the emergence of multipotent cancer stem cells (36-38) or envisioned as the pathological outcome of dysregulated pathways to justify the attainment of similar cancerous phenotypes (39). In this respect, many oncogenes induce senescence (40) and the process of EMT is sufficient to surpass it (41) and to acquire the cancer stem cell state from different phenotypes (19, 42). Furthermore, recent studies on carcinomas indicate that cellular senescence colocalizes with EMT (43). Therefore, in this contribution, the role of both processes is revisited to provide an alternative interpretation for the origin and progression of carcinomas in which the recovery of cellular plasticity is the main driver of carcinogenesis.

Carcinomas arise from epithelial tissues and exhibit a robust pattern of cellular and molecular events (44). In brief, the atypical hyperplasias are considered the precursors of the carcinomas *in situ*, that in turn *evolve* from well-differentiated tumors into poorly differentiated and highly metastatic cancers (44). Moreover, this multistep histological progression of carcinomas in humans is also recapitulated in murine models of chemical carcinogenesis (45). Hyperplasias are characterized by the presence of senescent cells (46) that show telomere attrition associated with replicative exhaustion (47) but are considered non-malignant tissues (48). Their progression to carcinomas correlate with their infiltration by cells of the immune system (49, 50) and a diminution of senescent cells (51). In turn, carcinomas tend to dedifferentiate and acquire aggressive behavior in a process accompanied by the gradual loss of epithelial features (44), while increasing the content of mesenchymal (52) and cancer stem cell biomarkers and the number of metastasis (53). Notably, the five-year survival rate in carcinomas exceeds ninety percent unless patients present metastasis or dedifferentiated tumors at diagnosis (54, 55). Remarkably, the increment of stromal cells (56) and EMT biomarkers (57) is an independent factor of overall poor prognosis in carcinomas (58).

The modern conception of senescence suggests that rather than a mechanism that evolves to halt tumorigenesis, is a type of cellular fate (16) in which cells acquire transient cellular plasticity (59) and instead

of being irreversible, is unstable and cells eventually emerge from it (60). Furthermore, the formation of sporadic carcinomas *in vivo* requires cellular senescence (61) and their pattern of hypomethylation has been considered primed for cancer behavior (62). Interestingly, the abrogation of senescence has been linked with the overexpression of mesenchymal transcription factors, the induction of EMT, and the adoption of carcinogenic and invasive potential (41). Besides, the process of senescence, inflammation, and EMT coexists in tissues with carcinomas (43) whereas the presence of biomarkers of stemness and inflammation has been involved in the acquisition of plasticity in senescent cells (63). In this respect, the concept of deregulated cellular plasticity as one of the main causes underlying carcinogenesis is gaining acceptance since modern techniques of lineage tracing are increasingly showing the interconvertibility of cellular phenotypes in the tumoral microenvironment.

Recent analysis indicates that epithelial cells from the parenchyma undergo EMT and account for most of the fibroblastic cells in the desmoplasia associated with the carcinomas (64). Likewise, in murine models, the majority of cancer-associated fibroblasts arise from EMT of epithelial cells *in vivo* and some acquire the genetic expression profile of cancer stem cells (65). Additionally, the process of EMT has been reiteratively linked with the generation of mesenchymal stem cells and cancer stem cells (22, 53, 65) that in turn might give rise to fibroblast, endothelial cells, pericytes, adipocytes, and macrophages in the tumoral microenvironment (22). After experiencing EMT, cells also harbor the potential to migrate (66) and undergo mesenchymal to epithelial transition (MET) to produce metastasis with epithelial phenotype upon exposition with the parenchyma of the lungs and bones (21, 67). Furthermore, cancer stem cells derived from EMT are able to reconstitute the entire tumoral mass along with its cellular heterogeneity (68). Moreover, cancer stem cells are not only resistant to chemotherapy and radiotherapy but induced after the exposition, and may lead to secondary cancers or tumor relapse (69). On this matter, modern perception of cancer considers the possibility that genomic instability, epigenetic reprogramming, or dedifferentiation allows the emergence of cancer stem cells that account for most of the features of the disease (36-38).

The hypothesis also considers findings from the primary cultures of normal epithelial cells since several observations suggest a generic order of events for the recovery of plasticity in cells that experienced replicative exhaustion. Namely, the process of spontaneous immortalization implies a discrete change in phenotypes that epithelial cells experience *in vitro* (70). During this process is observed the gradual loss of epithelial markers in response to replicative senescence from which eventually arise cells with a fibroblastic morphology that express the mesenchymal biomarkers (71). Current evidence shows that proinflammatory cytokines induce proliferation on epithelial cells and eventually their entry into cellular senescence (72). However, in response to increased concentration of interleukins, cells may undergo direct EMT and emerge with the morphology of fibroblasts and display the functional properties of migration, invasion, and stemness (72). Besides, the adoption of mesenchymal stem traits in cells derived from carcinomas was associated with the response to genetic damage (73). Overall, rather than consider the formation of sporadic carcinomas as the result of the continuous accumulation of aberrant traits in the genetic code, the premise of the hypothesis is that the tumorigenesis of epithelial tissues can be understood as the consequence of discrete changes in cellular phenotypes fostered by the influence cellular aging and inflammation on the machinery that controls the epigenetic profile. In essence, is acknowledged that senescent cells are prone to dedifferentiation and EMT epitomizes the process enabling the emergence of cells primed for carcinogenesis. In addition, the molecular mechanisms that might link both processes with the genesis of the sporadic carcinomas from hyperplasia are provided, along with their potential role in their progression into the advanced high-grade stages of the disease.

The hypothesis

Is proposed that cells in the epithelial hyperplasias are enabled to enter an endogenous cellular state with carcinogenic potential. Primarily, the involution of epithelial tissues associated with aging would be the result of cells that transdifferentiate mostly due to replicative senescence. Is argued that senescent cells

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become epigenetically susceptible to undergo further dedifferentiation mainly by EMT due to a combination of molecular, cellular, and structural events from which arises undifferentiated mesenchymal cells endowed with increased plasticity and carcinogenic potential. It proposes a model based on reported molecular interactions for the recovery of cellular plasticity in aged epithelial cells and provides an alternative mechanistic explanation for the role of mutations, senescence, inflammation, fibroblasts, stem cells, and EMT in carcinogenesis. Furthermore, suggest a potential rationale for the emergence of cancer-associated fibroblasts, myofibroblasts, metastasis, hybrid phenotypes, and cancer stem cells during the histological progression of carcinomas. The following describes the molecular endogenous process that might justify the dedifferentiation at the cellular level, and then, an attempt to explain the complex interplay that may occur during the genesis of the sporadic carcinomas in the histological context along with the mechanisms responsible for the discrete changes in cellular phenotypes that potentially account for the phenomenon of human carcinomas. In addition, considering recent insights from the differentiation trajectories in the normal breast and the emergence of resistance in the different molecular subtypes of breast carcinomas is envisioned a potential epigenetic landscape for its progression along with a rational alternative for therapy in the light of the insights derived from the model. Finally, a novel approach is presented to understand the unavoidable functional and structural degeneration of tissues during aging, and their increased vulnerability to malignant transformation when the process is associated with pathological levels of inflammation. Altogether, our perspective to comprehend the involution and carcinogenesis of epithelial tissues associated with aging may serve to inspire future experimental work and a more integrative approach to the study and management of chronic diseases.

Recovering the plasticity of epithelial cells

Carcinomas arise from epithelial tissues and represent over 85% of all malignant tumors diagnosed in adults. The most common cancers develop from the skin, breast, endometrium, prostate, colon, lung, pancreas, bladder, liver, and cervix (74). Broadly, epithelial tissues are constituted by the parenchyma composed of epithelial cells which provide the specialized functions within an organ, and the mesenchymal cells which produce the scaffold by the synthesis of the ECM (75). A series of reports have indicated that the epithelium-specific transcription factors with a conserved ETS domain are crucial for the morphogenesis, development, and preservation of the epithelial phenotype (76, 77). Moreover, the downregulation of the ETS specific of epithelium (ESE) family of proteins is sufficient for the loss of differentiation and the generation of carcinomas (77). In this regard, the transcription factors ESE-1 (78, 79), ESE-2 (80), ESE-3 (81), and PDEF (Prostate-derived Ets factor) (82) are reserved for epithelial cells and their suppression induces the emergence of the mesenchymal phenotype (75). Importantly, conditions that increase the expression of the zinc-finger binding transcription factor (Snail), the Snail Family Transcriptional Repressor 2 (Slug), the twist family bHLH transcription factor 1 (Twist1), the Twist-related protein 2 (Twist2), the Zinc finger E-box-binding homeobox protein 1 (ZEB1) and ZEB2 would promote the downregulation of the ESE proteins and the emergence of fibroblasts (83). The process by which epithelial cells undergo transdifferentiation into mesenchymal cells is called EMT and its part of the normal process of gastrulation in the early embryo development. Of note, mesenchymal cells migrate through the embryo for proper morphogenesis, and some undergo MET to originate the endoderm while others remain differentiated in the mesenchyme to generate the mesoderm (84). Hence, under certain conditions normal epithelial cells dedifferentiate and transdifferentiate in similitude to cells derived from carcinomas (85, 86). Considering the following substantial evidence, the hypothesis claims that cellular aging allows the recovery of cellular plasticity on terminal differentiated epithelial cells.

The generation of hyperplasias and the accumulation of senescent cells in epithelial tissues is related to the high proliferation rate required to sustain their functions (87). These lesions are considered the non-obligated precursors of the carcinomas (88) and are characterized by the presence of short telomeres and other features associated with cellular senescence (46, 89). In addition, senescent cells and the levels of p16 progressively accumulate with age (90) and correlate with a decline in the replicative capacity of epithelial

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tissues (91). Furthermore, the relationship between aging and cancer is highlighted by the incidence curves for most carcinomas since they rise after the age of 50 years and chances increase exponentially with each extra decade of life (92). Hence, the molecular process that cells undergo during senescence in hyperplasia is mechanistically linked with the fundamental causes of carcinoma development *in vivo* (93).

The molecular pathways activated in response to replicative exhaustion are similar to a DNA damage response (DDR) (94). The erosion of telomeres initiates a series of actions that would bring cell cycle arrest (94). As such, senescent cells display structures in the telomeres known as DNA repair *foci* that are also observed in response to DNA double-strand breaks (95). Their generation involves the phosphorylation of the histone family member X (H2AX) by the Ataxia telangiectasia mutated protein kinase (ATM) (96), the activation of p53, the Checkpoint kinase 2 (Chk2) (97), the Cyclin-dependent kinase inhibitor 1 (p21) (98), the Promyelocytic leukemia protein (PML) (99) and the epigenetic derepression of the locus of the inhibitors of kinase (Ink4b/ARF/Ink4a). The locus encodes the cyclin-dependent kinase inhibitor 2B (p15), the cyclin-dependent kinase inhibitor 2A (p16), and the alternative reading frame product of CDKN2A (p14) (90). Intriguingly, the activation of ATM also triggers the transcription nuclear factor kappa B (NF-κB) by the phosphorylation of the NF-κB essential modulator (NEMO) (73). In turn, this protein coordinates the secretion of cytokines, chemokines, growth factors, and proteases liberated by senescent cells (15, 100). In addition, senescent cells experience changes in the configuration of chromatin that are associated with genome instability (101) that might be also influenced by NF-κB since it binds the promoters of demethylases and conducts transcriptional derepression (102). For example, the histone H3 lysine-27 demethylase Jmjd3 (Jmjd3) depends on the direct binding of NF-κB to a cluster of three kB sites in its promoter and upon activation promotes histone demethylation leading to cellular plasticity (102).

Many oncogenic signals induce senescence in the first place and thereafter is observed the adoption of fibroblastic morphology by EMT with the upregulation of mesenchymal biomarkers (103, 104). Further, the overexpression of mesenchymal transcription factors is reiteratively linked with the suppression of cellular senescence through EMT and the acquisition of tumorigenic and invasive potential (41). Notably, the promoters of the mesenchymal transcription factors also contain binding sites for NF-kB (105), and the constant stimulation of Snail, Slug, Twist, or Zeb originate repression of the Ink4b/ARF/Ink4a locus and ETS proteins (106-108). Besides, the mesenchymal transcription factors bind and repress the promoters of the ESE proteins (109) whereas the suppression of the cellular senescence seems to be related to the activities of the polycomb proteins that modulate the structure of chromatin (110). Remarkably, the axis of NF-κB, Twist, and the proto-oncogene Polycomb Ring Finger protein 1 (Bmi1) resulted essential for the repression of the epithelial phenotype, the Ink4b/ARF/Ink4a locus, and to sustain the transcriptional signature associated with a mesenchymal stem cell (111). Interestingly, Bmi1 regulates stemness in breast cancer cells by the positive regulation of the homeobox pluripotency transcription factor (Nanog) expression through the NF-κB pathway (112). Therefore, seem plausible that senescent cells became prone to dedifferentiate by an endogenous molecular network that is set in motion due to the constitutive activation of the DDR and NF-kB. Hence, may fundamentally link aging and inflammation with carcinogenesis although from a different view since suggests a plausible mutationless mechanism by which a fully differentiated phenotype manages the recovery of cellular plasticity.

In line with those suppositions, the adoption of mesenchymal stem traits and malignancy in epithelial cells seem to require the presence of genetic damage (73) and inflammation (72). In addition, the NF-κB signaling pathway in carcinoma cell lines produces demethylation and the upregulation of genes normally expressed in the pluripotent stem cells (113). In the same way, the stimulation of IL-6 drives epigenetic changes dependent on NF-kB and DNA methyltransferases that resulted in epigenetic reprogramming and the emergence of cancer stem cells (114). Furthermore, the activation of NF-kB by IL-6 was sufficient to induce an epigenetic switch from breast immortalized cells to cancer stem cells in a single event of dedifferentiation (115).

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The transcription factor NF-κB is well known for its critical role in mediating responses to a remarkable diversity of stresses (116), however, is lately emerging as the central hub in the molecular network that coordinates the events of transdifferentiation induced by inflammatory cytokines and the generation of cancer stem cells (114).

In stem cells, plasticity is associated with transcriptional hyperactivity mediated by the combined effects of the polycomb proteins, DNA methyltransferases, and transcription factors on the configuration of the chromatin (117-119). In addition, the emergence of stemness and its maintenance is strongly influenced by several unspecific stressors such as the level of cytokines, oxygen, growth factors, mechanical forces, DNA damage, radiation, and antineoplastic agents (120-124). Therefore, stemness can be viewed as a cell state rather than a fixed phenotype (117). Furthermore, the normal biology of the stem cells has been implicated in most features associated with cancer. For example, their metabolism relies on glucose and glutamine to proliferate and is characterized by the conversion of glucose to lactate despite the presence of enough oxygen to sustain its complete oxidation (125, 126). In stem cells, the proteins p16 and p53 are downregulated (127, 128), while overexpressing process of DNA repair, detoxifying enzymes, and ABC transporters result in an increased threshold for apoptosis (129). Additionally, telomerase is reactivated and implicated in cellular immortality (130). Moreover, over long-term cultures, stem cells develop chromosomal instability (131) and possess constitutively high levels of NF-κB necessary to sustain the undifferentiated phenotype (132). Finally, stem cells self-renew or differentiate into several cellular phenotypes according to microenvironment cues (132), they survive the anoikis and exhibit an inherent ability to migrate, (133) along with intrinsic capabilities to evade the immune response (134). Therefore, it can be argued that senescent cells resemble some aspects of stem cells. For example, they exhibit major changes in the chromatin configuration mediated by the effects of the polycomb proteins (135) and an increment in the transcriptional capabilities associated with demethylation and other epigenetic mechanisms that might underlie their susceptibility to malignant transformation (62). Therefore, is plausible that in response to molecular damage, inflammation triggers an epigenetic reprograming in aged epithelial cells and enables the recovery of cellular plasticity with the adoption of cellular states with cancerous behavior (Fig.1). Hence, is suggested that senescent cells are a *step closer* to stemness, but also, their presence in epithelial tissues increases the tendency to neoplastic transformation due to structural and endocrine disruption. In the following, is proposed a potential series of events that might shape the histological carcinogenesis of the epithelial tissues *in vivo*.

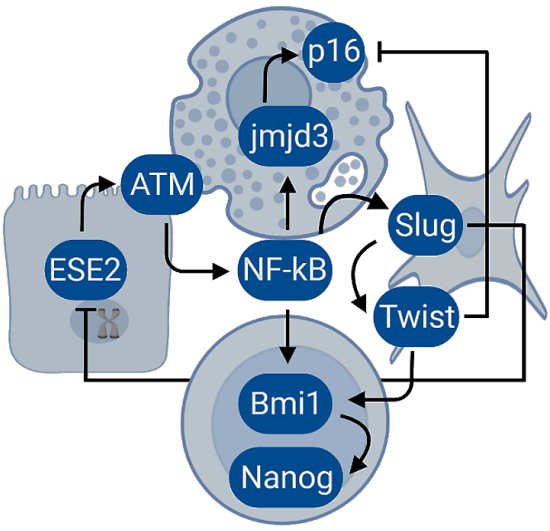

Fig. 1 Molecular interactions potentially involved in the recovery of cellular plasticity in aged epithelial cells. The activation of this pathway may enable epigenetic switches into mesenchymal and stem phenotypes. In addition, in response to oscillations in endogenous or microenvironmental stimulus, the aged epithelial cells might give rise to several phenotypes and lead to tumoral heterogeneity and metastasis

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The progression of epithelial hyperplasias into carcinomas

The infiltration of lymphocytes to hyperplasias is repeatedly associated with their malignant progression (136-138). The attraction of immune cells to tissues that present senescent cells is comprehensible since their secretions include the monocyte chemoattractant protein 1 (MCP-1) and matrix metalloproteinases (MMPs) that stimulate the migration and infiltration of monocytes, lymphocytes, and NK cells along with the degradation of the ECM, proteinase inhibitors, cell surface receptors, and cell-cell adhesion molecules (139). In turn, the activation of macrophages may drive an increased expression of proinflammatory cytokines and MMPs (140), both associated with the induction of EMT (18, 19) and the generation of cancer stem cells (19, 141). The cytokines tumor necrosis factor-alpha (TNF-α), the transforming growth factor-beta (TGF-β), and the interleukin-6 (IL-6) which are some of the most studied inducers of EMT (142-145), all converge in the activation of the transcription factor NF-κB (143, 144, 146). Regarding MMPs their effects on induction of EMT have been also documented to be mediated via the activation of the mesenchymal transcription factors by NF-κB (147). Likewise, cell detachment from the ECM, the basal membrane, or cells favors dedifferentiation via EMT (18), whereas the signaling pathways activated by mechanical stress, such as the focal adhesion kinase (FAK), the transcription factor Yes-associated protein (YAP) and the transcriptional co-activator with PDZ-binding motif (TAZ) also showed to generate cancer stem cells (148). Another mechanism potentially involved in the progression of hyperplasias is the coupling of the integrin and Rac kinases with the NF-κB pathway through the IKK complex (149). Hence, senescent cells might adversely influence the differentiation and behavior of neighboring cells by disrupting the endocrine and structural microenvironment which along with their recovered cellular plasticity may foster the malignant transformation of epithelial tissues affected with hyperplasias.

Both processes, senescence and EMT are associated with increased activity of NF-κB (142, 150) and linked with events of early development and with the recovery of cellular plasticity (59, 151, 152). In line with those observations, the hyperactivation of the NF-κB pathway in tumors is comprehensible since it responds to structure or endocrine changes in the environment, including damage in the stroma, and the levels of cytokines, radiation, oxidative stress, hormones, and growth factors or due to intracellular molecular damage (153). Altogether, the structural disruption in tissues with the presence of senescent cells may bring constant inflammation to facilitate events of dedifferentiation that manifest as cells with cancer behavior. In a sense, in the beginning, senescent cells are primed for cancer behavior due to endogenous damage, but eventually, their presence in tissues produces an aberrant microenvironment that may promote and amplify the dedifferentiation of non-aged cells via extracellular signals but essentially through the same molecular interactions (summarized in Fig.1).

Consistent with those premises, the adoption of the mesenchymal-stem phenotype in cells from carcinomas has been linked with ATM and NF-κB activation in response to DDR with the production of IL-6 that promotes a persistent proliferative signaling and the fibroblastic shape (73). Intriguingly, fibroblasts detected in preneoplasic lesions and chronic inflammatory conditions have been shown to express the markers of senescence (154), and the alpha-smooth muscle actin (α-SMA). This last protein is associated with myofibroblasts, which are mesenchymal cells that harbor enhanced plasticity and multipotency (155). In the case of high-grade carcinomas, is typical the loss of epithelial features and the increment of the mesenchymal and cancer stem cell biomarkers (53, 57, 58). In addition, the gain in the stromal compartment is an independent factor of overall poor prognosis and the presence of metastasis (56-58). Hence, is theorized that the combination of endogenous molecular damage and structural tissue disruption promotes higher levels of constitutive inflammation that favors the attainment of a mesenchymal and plastic phenotype that manifests as epithelial dedifferentiation and explains the stromal enrichment observed during the histological progression of carcinomas.

Accordingly, the increased levels of proinflammatory cytokines *in vivo* have been linked with EMT and the accumulation of cancer stem cells within tumors (19). Furthermore, fibroblasts (65) and myofibroblasts (64) in carcinomas are mostly derived from epithelial cells that undergo EMT resulting in mesenchymal cells with

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a higher degree of plasticity and multipotency (155), lower DNA methylation (156) and some might acquire the genetic expression profile related with the cancer stem cells (65). Besides, cancer-associated fibroblasts are characterized by increased NF-κB expression and the secretion of TGF-β, IL-6, MCP-1, and MMPs. Hence, fibroblasts detected in the tumoral microenvironment are traditionally viewed as cells actively promoting the inflammation, EMT, metastasis, angiogenesis, and the enrichment of cancer stem cells (157).

The mesenchymal cells produced by EMT express the pluripotent genes SRY-Box Transcription Factor 2 (SOX2), Nanog, the octamer-binding transcription factor 4 (Oct4), and the neurogenic locus notch homolog protein 1 (Notch1) (31, 158). Noticeably, the cellular plasticity endowed by inflammation not only activates the EMT of epithelial cells but upon enough stimulation the endothelial cells, monocytes, fibrocytes, pericytes, adipocytes, and local fibroblasts can dedifferentiate into myofibroblasts (159, 160). The adoption of the *fibroblastic program* confers cells the intrinsic potential to then differentiate into several subtypes of mesenchymal and non-mesenchymal lineages (161, 162). Even normal fibroblasts display transcriptional diversity and heterogeneity relative to the mechanical forces that experience due to structural changes, position, and the endocrine milieu in different tissues (161), and under appropriate conditions, they can differentiate into adipocytes, chondrocytes, osteocytes, hepatocytes, neurons, myocytes, or pancreacytes (163, 164). In addition, cells in the mesenchymal program can migrate and infiltrate into damaged tissues, in which they may differentiate into fully functional cells (165, 166), but might also generate tumors (167, 168). Likewise, the formation of metastasis is understood as cells from tumors that undergo EMT and then migrate until the reversion of the process in response to microenvironmental changes by MET that re-enables the adoption of the epithelial phenotype (21, 169). It has been demonstrated that the reversion of EMT involves the interaction of cells with the parenchyma of the lungs and bones that downregulate the mesenchymal transcription factors allowing the recovery of the epithelial phenotype (20, 67).

Related findings suggest a requirement for higher levels of proinflammatory cytokines to sustain the fibroblastic shape, the malignancy, and stemness in cells from carcinomas (73). Accordingly, the suspension or diminution of inflammation resulted in the reappearance of the epithelioid morphology (72, 170). Further, the activity of Twist1 and Slug seems necessary for the overexpression of Bmi1 and to retain the stemness and invasiveness. In the same way, the inhibition of the mesenchymal transcription factors results in the emergence of the luminal (epithelial) phenotype (171). Altogether, the endogenous tendency of the most malignant subtypes of carcinomas to adopt a basal (fibroblastic) shape derives from DNA damage that in turn generates a permanent ATM activation and constitutive higher levels of NF-κB, secretion of cytokines, and the acquisition of the features of a mesenchymal stem cell with malignant behavior (73). Noteworthy, their invasive potential and disorganized growth have been associated with genes that require the activity of NF-κB (172). Intriguingly, the combined effect of an artificial ECM and the chemical interference of the inhibitor of nuclear factor-κB (IκB) kinase (IKK) complex was able to restore the epithelial phenotype, the formation of organized clusters along with the suppression of the malignancy and motility (172).

Nowadays is increasingly accepted the major role of the cell microenvironment in cellular plasticity (149, 172). Furthermore, the molecular regulatory networks that coordinate the events of transdifferentiation and the generation of cancer stem cells have been increasingly elucidated. Expectedly, they show convergence into the activity of NF-κB and its influence on the regulators of the epigenetic control (73, 114, 142, 150). In addition, is considered that stemness remains elusive to describe *in vivo* since requires particular structural or endocrine conditions (173). Additionally, its emergence and maintenance are strongly influenced by the dynamics of cell growth, that in turn naturally induce cellular heterogeneity due to cell-cell interactions, and the oscillatory level of cytokines, oxygen, growth factors, and mechanical forces (174-176). On this subject, the concept of niches captures the notion of stem cells as entities highly dependent on microenvironment conditions, since it describes domains in which cells and their structural and endocrine interactions result in stemness (173). The fact that the maintenance of stem cells *in vitro* requires serum-free media enriched with growth factors such as the TGF-β, TNF-α, and hypoxic conditions to avoid their differentiation illustrates the

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challenge that has been to define their nature (177). Moreover, the comparison of cancer stem cells and embryonic stem cells revealed convergence at transcriptional (178), and functional levels (179). Therefore, it has been suggested that the only difference between the normal and the cancer stemness lies in the tumor microenvironment (180). Recent evidence shows the existence of hybrid phenotypes within carcinomas with the ability to regenerate tumors with the original cellular heterogeneity (181). This finding is expected considering the molecular biology of stem cells, since their transcriptional hyperactivity results in the expression of markers from several lineages (119). Hence, is tempting to speculate that the epithelial carcinogenesis at its core is fostered by gradual transcriptional derepression in aged or damaged cells which in conjunction with the microenvironmental cues drives and shapes the histological progression of carcinomas. Additionally, in the setting of the high-grade tumors is implied deregulated plasticity and access to stemness that correlates with the adoption of the apocrine and basal phenotypes in the advanced phases of the neoplasia that arise from the epithelial tissues (Fig. 2).

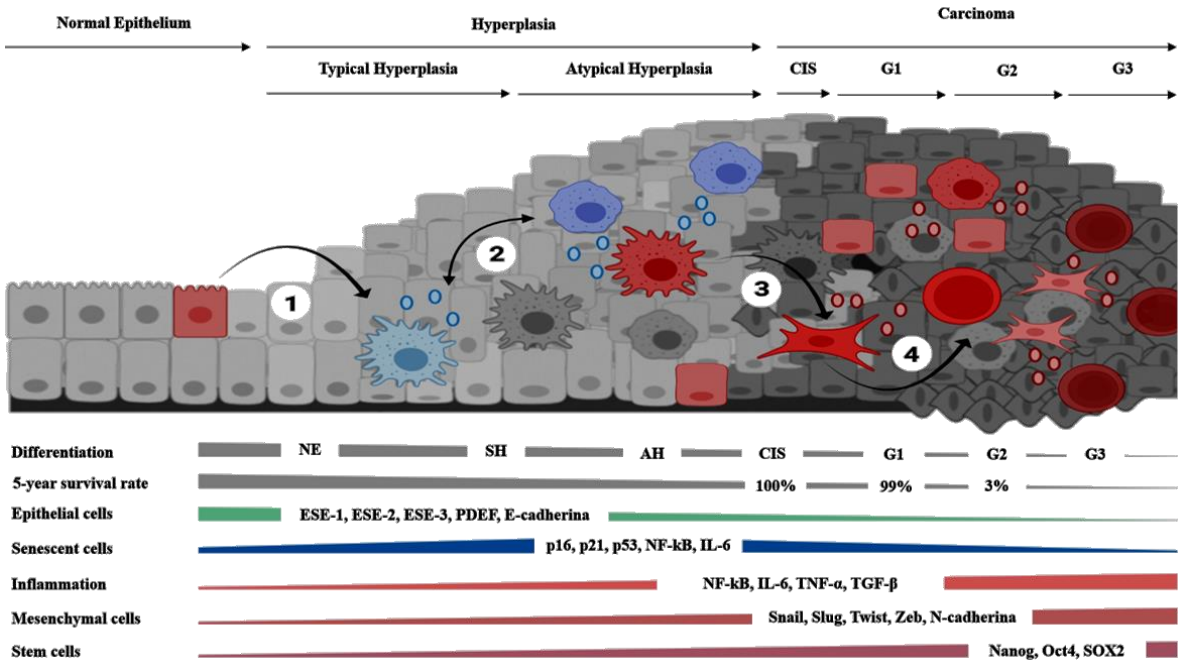

Fig. 2 Molecular and cellular processes that may shape the histological progression of carcinomas. The hypothesis considers that epithelial tissues exposed to proliferation eventually become enriched with senescent cells and conduct into the hyperplasia (1). In this setting, cytokines generate the infiltration of immune cells (2) that potentially induce EMT in senescent cells (3). After the EMT produced by inflammation cells acquire the fibroblastic program and cellular plasticity that is evident with the emergence of stem biomarkers (4). The influence and fluctuations of the stimulus due to changes in the tumoral microenvironment may give rise to cellular heterogeneity. For example, the interactions with stroma, cells, parenchyma, and the endocrine *milieu*, including the concentration of oxygen, nutrients, and growth factors or the reduction in the levels of inflammation would originate the emergence of epithelial, fibroblastic, myofibroblastic, hybrid or stem phenotypes. However, in the context of the high-grade carcinoma, the undifferentiated tumorigenic state is preferentially sustained by the burden of endogenous molecular damage, and an increased inflammatory microenvironment that includes tissue disruption. Hence, the apocrine and basal tumors lose the glandular architecture since the mesenchymal and pluripotent transcription factors are constitutively activated explaining the increment in stromal content along with the metastatic and aggressive behavior. Bars illustrate the degree of differentiation and their relationship with survival as well as the molecular biomarkers that characterize each cellular process with their relative abundance during every histological stage in the progression of carcinomas. NE, Normal epithelia, SH, Simple hyperplasia, AH, Atypical hyperplasia, CIS, *Carcinoma in situ*, G, grade

The events underlying the histological progression of carcinomas *in vivo* remain partially understood. Here was described a plausible molecular mechanism by which aged cells recover cellular plasticity due to constant activation of DNA damage response and inflammation that promote dedifferentiation and prone the affected tissues with hyperplasias to progress into sporadic carcinomas. Instead of considering that the

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cancerous phenotype is the result of mutations or selective gene modulation, is proposed that the replicative cellular senescence leads to transcriptional derepression that enables plasticity and discrete changes in cellular phenotypes. Is hypothesized that the chromosomal anomalies in senescent cells and the immune infiltration in response to secretory phenotype are the primordial drivers of cancer, and explain its long relationship with genetic damage, aging, and inflammation. Hence, this implies a long latency period, which is normally seen in the generation of most sporadic carcinomas and the multistep histological process of carcinogenesis since hyperplasia provides the initial conditions for transformation. However, their successive progression into carcinomas seems to require a higher burden of senescent cells and inflammation to epigenetically increase the chromatin derepression. Those conditions in turn may give rise to the histological atypia and produce a permissive microenvironment for dedifferentiation and transformation.

Despite that is postulated that initially the cancer behavior is expected from senescent cells undergoing EMT in the hyperplasia, is foreseen that in the tumoral microenvironment associated with high-grade carcinomas several phenotypes might dedifferentiate and contribute to tumorigenesis. Therefore, in the setting of the apocrine or large-sized tumors, the effects of inflammation and tissue disruption over the differentiation state of cells may account for the aggressive and self-sustained malignant behavior of the advanced carcinomas. Is assumed that the permanent activation of these conditions conducts the gradual loss of the epithelial characteristics that coexists with structural changes, an increment of the stroma, the biomarkers of inflammation, EMT, and cancer stem cells in the aggressive and metastatic high-grade carcinomas. According to the molecular mechanisms reviewed, is comprehensible that under a certain threshold of endogenous molecular damage and tissue disruption, epithelial tumors evolve into the autonomous entities that characterize the invasive and lethal course of the advanced carcinomas.

Demystifying tumor heterogeneity and resistance

Broadly, the advanced phases of carcinomas remain untreatable, and the management of stage I to III tumors result in their eventual progression with the development of the incurable metastatic disease (182). In addition, most antineoplastics drugs and radiotherapy are clastogenic and carcinogenic (7, 183) and the deterioration post-therapy has been estimated in 15 years of cellular aging (184). Hence, those who survive cytotoxic therapies experience the emergence of secondary cancers or tumor relapse, extensive organ fibrosis, accelerated aging, and early onset of its associated diseases (7, 183, 185-187). Moreover, substantial evidence suggests that therapy is an active player in the changes that undergo the malignant and premalignant cells. In this regard, chemotherapy and radiotherapy not only generate DNA damage that results in tumoral shrinkage and cell death associated with the partial or complete responses, but they also simultaneously trigger senescence, inflammation, EMT, and stemness in the exposed cells that manifest with the adoption of different epigenetic profiles and increased aggressiveness (23, 43, 121, 188, 189).

Recent insights from breast carcinomas are consistent with the notion of epigenetic switches rather than selection and mutations as the driving force of malignancy and resistance (190). Furthermore, it has been suggested that instead of targeting multiple signaling pathways associated with resistance in the heterogenous tumoral microenvironment a better approach would be to prevent the entry of cancer cells into cellular states that allow them to survive therapeutics (191). This section brings evidence from breast neoplasia that links cellular aging and inflammation not only with the genesis of carcinomas but also with their heterogeneity, progression, resistance, and relapses after therapy. In addition, considering the insights derived from the model and the current state of knowledge in breast epithelial biology and its neoplasms is proposed an epigenetic landscape that gives rise to the molecular heterogeneity and progression in breast carcinomas despite the application of therapy.

According to morphological features, breast carcinomas exceed the 20 subtypes, however, over 90% are histologically classified as invasive ductal carcinoma or lobular carcinoma. The rest are considered rare,

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such as the medullary, metaplastic, apocrine, mucinous, cribriform, tubular, neuroendocrine, and pleomorphic (192). Regarding histological grade, the assessment of the degree of differentiation is used to stratify breast cancers into grade 1, for slow-growing and well-differentiated tumors; grade 2, for moderately differentiated; and grade 3, for highly proliferative and poorly differentiated (193). Based on gene expression profiles, four molecular subgroups are well established, named Luminal A, Luminal B, HER2+, and triple-negative breast carcinomas (TNBC) (194). In general, Luminal A and B comprise over 70% of newly diagnosed breast cancer cases, express hormonal receptors, and have characteristics of luminal epithelial cells of the breast. The HER2+ variant represents 20% of newly diagnosed breast cancer cases and is characterized by high expression of the protein HER2 and loss of the hormonal receptors in tumors of greater histological grade (195), but they also can be classified as luminal type (196). In the case of the TNBC they account for approximately 10% of all cases and lack the expression of the hormonal and HER2 receptors, the luminal differentiation markers, are claudin-low, and are considered the most aggressive subtype of breast carcinoma (197). These tumors display from the beginning strong resistance to chemotherapy and radiotherapy (198), histologically, they show high-grade, basal markers, fibrotic zones, pushing borders of invasion, and lymphocytic infiltration (199), with vimentin and NF-κB expression (200). Considering the gene expression profile of TNBC, they display signatures that correspond to myoepithelial markers and DNA damage responses, overexpression of immune signal transduction pathways, EMT and mesenchymal stem genes, and a subgroup enriched in hormonal pathways (201). Interestingly, these findings appear consistent with the postulates described in Fig. 2 for the molecular process underlying the emergence of high-grade carcinomas.

The differences in the molecular subtypes of breast carcinomas have been exploited to assess prognosis as well as a strategy for therapy selection, however, responses are temporal and followed by relapse. Interestingly, the acquisition of resistance and malignancy is accompanied by changes in the original molecular profile (202-204). Besides, the TNBC tumoral masses contain cells that correspond with the other subtypes, with an estimated composition of 50% basal-like, 30% claudin-low (*both considered TNBC*), 9% HER2+, 6% luminal B, 5% luminal A and remnants of normal like tissue (201). Furthermore, cumulative evidence demonstrates the interconversion among breast cancer subtypes and is illustrated by the emergence of resistance. For example, the luminal subtypes become insensitive to the antiestrogen tamoxifen by EMT and the adoption of the epigenetic profile of the mesenchymal stem cell (202). Similarly, breast cancer patients whose primary tumor was HER-2 negative turn positive during cancer progression (203). Likewise, HER2+ breast cancers evolve into TBCA tumors during the treatment with trastuzumab, the humanized antibody directed against the extracellular domain of the tyrosine kinase receptor HER2. The process of resistance involves EMT with and independence from the ERBB family signaling pathway. Hence, drugs induce EMT and the emergence of the TNBC phenotype along with increased resistance, stem cell features, and metastatic potential (203). On this matter, the analysis of primary breast cancer biopsies that include triple-negative specimens revealed enrichment of cancer stem cell signatures after chemotherapy (205). Notably, the molecular responses associated with the resistance of TNBC found an increment in the expression of beta-galactosidase, p16 (206), and the proportion of polyploid senescent cells in tumors that failed to respond to neoadjuvant chemotherapy (207). Moreover in a pre-clinical model of TNBC was demonstrated a causal relationship between therapy-induced senescence and the generation of chemoresistant stem-like populations (208). Also consistent, TNBC cells exposed to doxorubicin induce the EMT transcription factors to increase their resistance to treatments (209). Tumors conformed mostly by triple-negative cells are the most lethal subtype of breast cancer and lack effective therapeutic options (198). Chemotherapy, radiotherapy, and targeted drugs fail to improve prognosis; and the progression-free survival remains low with a median of 7 months (210). TNBC tumors poorly respond to tamoxifen, trastuzumab, or Atezolizumab, a humanized monoclonal antibody against the programmed death-ligand 1 (PD-L1), that negatively regulates the cytotoxic T-lymphocyte activation (210).

Understanding the origin of carcinomas has the potential to postulate novel approaches to prevent and treat neoplasia. Altogether our model and the reviewed evidence suggest the existence of few endogenous

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cellular states driving carcinogenesis. In addition, studies indicate that senescence and EMT enable not only the progression from hyperplasia to carcinoma but its *evolution* by dedifferentiation into higher grades in which the stem or basal-like phenotypes are naturally resistant to current therapeutics.

Providing further support for those statements, in a recent transcriptomic characterization of the normal breast tissue was proposed that the basal mammary stem cells differentiate either into myoepithelial cells or into a luminal progenitor, which gives rise to the two distinct luminal cell types, one secretory and the other hormone-responsive (211). Besides, they found correspondence between the discovered normal cellular states with the molecular subtypes of breast carcinomas (211). On the other hand, the exposition of immortalized breast epithelial cells to IL-6 is sufficient to induce an epigenetic switch mediated by NF-κB and the emergence of TNBC like cells (115). Thus, appears that any attempt to treat or prevent cancer that produces toxicity has the potential to result in dedifferentiation with the adoption of preexisting and robust cellular states.

The mechanisms involved are the DNA damage response (73), the disruption of tissue that results in constitutive higher levels of inflammation, and the acquisition of stemness (73, 149). In accordance, TNBC tumors exhibit enriched expression of DDR, inflammation, EMT, and stemness (201). In addition, the adoption of the fibroblastic shape in cells derived from carcinomas seems to require inflammation (72, 170), the DNA damage response, and the activity of ATM, NF-κB (73), and the EMT transcription factors (171). Consistently, most TNBC cell lines are assigned as basal or mesenchymal-like subtypes and display the expression of EMT and stem markers (212). Therefore, seems plausible that during the malignant transformation and carcinoma progression cells adopt a preexisting cellular state within the boundaries of their trajectory of differentiation according to the type of stimulus. Is speculated that cellular senescence and EMT allow those epigenetic switches and explain the evolution of luminal or HER2 subtypes of breast cancer into the lethal TBCA tumors (Fig. 3). Importantly, the connection of damage and the NF-κB signal with the activity of demethylases and the mesenchymal transcription factors provides a molecular mechanism to explore novel approaches for the management of carcinomas. In other words, the model suggests that targeting the degree of malignancy with drugs that modulate inflammation may restore the epithelial differentiation of high-grade tumors along with a diminution in their malignancy in spite of the endogenous molecular damage and the aberrant extracellular signals in the tumoral microenvironment.

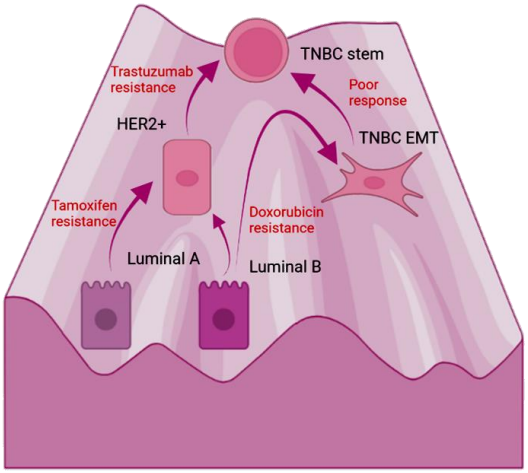

Fig 3. The potential landscape for breast cancer progression and epigenetic switches involved in the emergence of resistance. The recent characterization of the transcriptomic profiles in the normal breast suggests the existence of five cellular states derived from a basal stem cell that differentiates into a myoepithelial cell or a luminal progenitor, from which arises two types of luminal cells. The information from the differentiation pathway was used to illustrate the cellular heterogeneity and their relative hierarchy within the normal breast. Then, breast cancer subtypes were located according to their molecular profile in the basin of the normal transcriptional related counterpart to highlight that complexity and the heterogeneity of breast carcinogenesis might be understood as the reversion of differentiation. Finally, some of the reviewed events of dedifferentiation in response to cancer-therapy are depicted in purple arrows. Remarkably, the process of cellular senescence and EMT are involved in triggering the epigenetic switches among the molecular subtypes of breast cancers

Leukemias and hematological disorders are naturally understood as diseases of immature lymphoid or myeloid cells, hence, the implementation of differentiation therapy seems reasonable (213). Conversely, solid tumors are neither considered cancers generated by dedifferentiated precursor cells nor able to

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differentiate due to their aberrant genetic code (214). However, according to our model, cancer progression can be slowed, and survival improved if therapy focuses on downmodulation of inflammation since would result in a partial recovery of the histological differentiation and the prevention of aggressive behavior.

Consistent with that view, the combined effect of an artificial ECM and the pharmacological inhibition of NF-κB restores the epithelial phenotype, and the organized growth while preventing the malignant phenotype of breast cancer cells (172). Accordingly, the role of the ECM in the induction of a normal phenotype in the mammary epithelial cells was demonstrated illustrating the major influence of tissue architecture over the genotype and behavior (215). Similarly, the inhibition of LIF/JAK1/STAT3 and NF-kB signaling pathways induced the differentiation of cancer stem cells from hepatocellular carcinoma and inhibited their self-renewal and tumorigenic capacity in a murine model (216). Moreover, the modulation of the NF-kB signaling and the suppression of the activities of the polycomb protein EZH2 resulted in enhanced differentiation of nasopharyngeal carcinoma cells *in vitro* via epigenetic mechanisms (217). The reviewed evidence suggests that the observed regression of epithelial tumors by their implantation in normal tissues *in vivo* (218) involves the effect of a normal ECM and epithelial cells on the activity of NF-kB that upon downregulation partially restores cell differentiation.

From the atypical hyperplasia to the higher-grade carcinomas, the inflammation associated with the genetic damage of aged cells appears to drive the carcinogenesis in the epithelial tissues by triggering cellular plasticity and dynamical events of dedifferentiation and transdifferentiation that may underlie tumoral heterogeneity, progression, and resistance. Despite breast carcinomas have been largely considered from different molecular and cellular origins or promoted by several genetic alterations, tumors intrinsically possess the other variants that in turn show correspondence with few preexistent cellular states in the normal breast tissue. Furthermore, during progression or in response to cancer therapy seems that breast cancer cells undergo epigenetic switches from one cellular state into another according to the stimulus. Therefore, cellular senescence, inflammation, and EMT might be involved not only in the malignant transformation of the epithelial hyperplasias into carcinomas *in situ*, but also, in the acquisition of an increasing degree of dedifferentiation during the progression of carcinomas.

Considering the reviewed evidence is plausible that TNBC entities corresponded not only with cancers originating from the basal mammary stem cells or in the myoepithelial cells but reflect the behavior of breast cells in those conditions of molecular and structural damage that prompt the emergence of the robust mesenchymal or basal phenotype primed for the lethal cancer behavior that is resistant to current therapeutics. In the light of the mechanistic role proposed for cellular aging and inflammation in carcinogenesis, seems plausible that failure in antineoplastic therapy results from the link of adversity and molecular damage with transcriptional derepression and stemness. Hence, cytotoxic drugs or radiotherapy foster an epigenetic switch in the surviving cells into a more resilient cellular phenotype. Additionally, is comprehensible the emergence of aggressive tumor relapses since clastogenic events derived from them foster higher levels of inflammation and plasticity. Interestingly, the adoption of mesenchymal lineages substituting the epithelial phenotypes suggest a generic principle for cell behavior in terminally differentiated cells once they experienced replicative cellular senescence or non-lethal adversity.

A misunderstood process of development

Developmental biology studies the mechanisms that govern the development of organisms from fertilization to senescence. In this framework, organs experience involution during normal aging characterized by calcification, steatosis, and fibrosis that are associated with replicative exhaustion and cellular senescence (219). Interestingly, fibroblasts derived from the process of EMT possess the potential to differentiate into adipocytes or osteocytes (22) whereas the activities of the mesenchymal transcription factors have been involved in the dedifferentiation driving the fatty change (220), calcifications (221), and

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the fibrosis of tissues (222). Importantly, progressive organ fibrosis is a major cause of morbidity and mortality and the therapeutic options are handicapped by an incomplete understanding of its origin (223). In addition, accumulating evidence attributes to EMT or related events of transdifferentiation the fibrosis of vessels, heart, liver, kidney, and pancreas (224, 225). In similitude to cancer, despite the current multitarget approaches to cope with cardiovascular diseases, and diabetes *mellitus*, they remain the principal causes of morbidity and mortality among adults in industrialized countries (226). Similarly, cellular senescence is associated with the functional cellular decline observed in chronic diseases, for example in the inability of senescent vascular endothelial cells to generate nitric oxide and regulate the coronary vascular tone associated with hypertension (227) whereas the defective insulin secretion in senescent pancreatic beta cells impairs the regulation of glucose levels in diabetes *mellitus* (228). Given the revised mechanisms is theorized that most chronic diseases are the result of the functional impairment of organs due to degeneration driven by cellular senescence and inflammation which promote events of transdifferentiation into mesenchymal lineages (Fig.4).

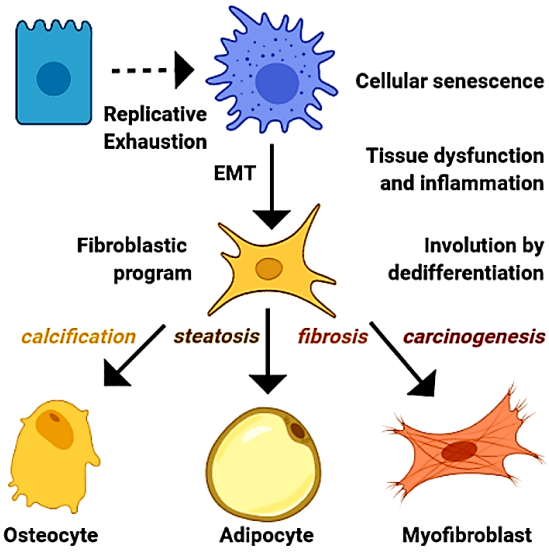

Fig. 4 The model proposes to understand chronic diseases as the result of tissue dedifferentiation initiated by cellular senescence. The molecular and cellular events reviewed for epithelial carcinogenesis appear also involved in the susceptibility of aged cells to dedifferentiate into mesenchymal lineages and explain the tendency of organs for calcification, steatosis, and fibrosis once they experience replicative exhaustion or inflammation. Those processes might underlie the observed dysfunction and the increased tendency of tissues for the malignant transformation that is associated with aging

Conclusion

The definitive mechanistic basis of the connection between DNA damage, aging, inflammation, and the origin of carcinomas remains unclear. However, is conceived that the increased sensibility in the technologies of lineage tracing will eventually cope with the dynamic interplay between microenvironment signals, endogenous perturbations, and chromatin remodeling that altogether are responsible for the mapping of the genotype to phenotype and cellular behavior that has been challenged our attempts to understand cancer. In this contribution was envisioned a model to explain the conserved pattern of molecular and cellular events observed during the histological progression of carcinomas and the rationale behind the reiterative emergence of the cellular phenotypes involved in the process. In addition, the model presented for the origin of carcinomas intuitively provides a plausible mechanistic explanation for the underlying causes of calcification, fibrosis, and steatosis that characterizes the degeneration, the loss of function, and in some cases the transformation of tissues during aging from a molecular perspective. Is postulated that cellular senescence would precede the onset of most chronic diseases. Then, inflammation and infiltration of the affected tissues may accelerate their degeneration by increasing their susceptibility to transdifferentiation. Finally, the adoption of mesenchymal phenotypes would be promoted by telomere attrition or tissue disruption leading to parenchyma degeneration and increased stromal content. It could be considered that the adoption of mesenchymal lineages reflects the behavior of cells with telomere

attrition on an endocrine milieu defective in stroma, hormones and growth factors since epithelial cells are highly dependent on ligands produced by other specialized cells and are fine-tuned by structural interactions. Therefore, aging implies the adoption of mesenchymal and more robust cellular states that are deprived of normal functions and manifests as the onset of chronic diseases. A logical consequence of the hypothesis suggests that conditions promoting and sustaining the emergence of myofibroblasts would foster the malignant transformation of tissues since cells in that state are endowed with plasticity and primed for tumorigenesis and metastatic behavior. Accordingly, any attempt to cure cancer that involves the induction of senescence, inflammation, or EMT would result in a temporal remedy followed by organ fibrosis, the worsening or the onset of chronic diseases, and the eventual emergence of tumors with increased malignancy. Altogether, the loss of genomic stability due to replicative exhaustion seems to originate degeneration of tissues by dedifferentiation into more robust but nonfunctional mesenchymal cells. Hence, implies a possible molecular link of most chronic diseases in which the same conserved events direct the dedifferentiation of tissues. According to this view, the likelihood of tumorigenesis seems preventable by downregulation of inflammation despite the unavoidable molecular aging and suggests a rational approach to cancer therapy.

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