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Review

Origin of carcinoma associated fibroblasts

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Abbreviations: CAF, cancer associated fibroblasts

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Recent evidence on the genomic integrity of non-malignant cells surrounding carcinoma cells has reinvigorated the discussion about the origin of the altered phenotype exhibited by carcinoma associated fibroblasts. Many hypotheses have been proposed for the origin of these altered cells, including standard connective tissue acute phase and stress response, fibroblast senescence, reciprocal interactions with the cancer cells, fibroblast specific somatic mutations, differentiation precursors and infiltrating mesenchymal stem cells. Here we review the definition of CAF phenotype and the evidence for each of those hypotheses, in the context of our current understanding of cancer etiology.

Attempts have been made to reach the goal of medical art—the prevention and cure of disease—by many different paths. New and reliable opportunities have become practicable as our knowledge of the nature of the different diseases has widened (Nobel prize committee presentation speech of the 1945 award for the discovery of Penicillin). One recent discovery that offers an opportunity for novel treatments of cancer involves the cells that are adjacent to epithelial cancer cells, collectively termed stromal cells, and particularly for this review, carcinoma associated fibroblasts (CAFs).[1-5] CAFs are different from resident fibroblasts of normal tissue in both molecular constitution as well as their functional impact on the neighboring epithelial cells. In animal models of prostate and breast cancer, non-malignant oncogene-expressing epithelial cells can become malignant when surrounded by fibroblasts that are either oncogene induced, or derived from a primary carcinoma mass.[1] Stroma encoded genes that may modulate the oncogenic potential of adjacent epithelia have been identified,[2,3] some of which result from signals received from the tumor and some are driven by somatic events within the fibroblast itself. Excellent reviews have been written on the nature of these cells, and their effects on cancer.[4-8] In this review we focus on the hypothetical origins of CAFs. Recent evidence shows that unlike cancer cells, where many changes occur via somatic mutations, the changes in cancer neighboring cells do not stem from somatic mutations.[9,10] We will therefore try to consider the reason for this mechanistic disparity between cancer cells and their neighboring cells. "In describing genetic mechanisms, there is a choice between being inexact and incomprehensible" (Nobel prize committee presentation speech of the 1965 award for the discovery of transcription regulation). In this review we shall try to be as inexact as conscience permits, in order to consider as many hypothetical mechanisms as possible for the emergence of CAFs. This aspect of cancer has long been appreciated (desmoplastic stroma[11-13]), and has been broadly associated with a poorly differentiated tumor cell phenotype and worse patient outcome[14-17] both in terms of metastatic potential as well as resistance to treatment. Therefore, the origins of CAFs will be considered in both the patient' body as well as from an historical point of view.

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Two Parallel Schools in the Research of Cancer Etiology

As research tools developed to allow us to observe smaller and smaller scales of biological structures, it was gradually realized that deformation is the common denominator of a multitude of events in the course of malignancy. Firstly, at the tissue architecture cellular scale in the way cells align relative to neighbors to form tissues, and migrating cells such as inflammatory cells infiltrate the tissue, in the cellular and nuclear morphology and, as noticed by Bovery,[18] in the molecular scale of genomic integrity. The cause and effect relationship between the molecular genomic level and that of the cellular level fits the paradigm of nature versus nurture conflict of perspectives, and not surprisingly is the focus of substantial debate that perpetuates along the history of cancer research.

Genomic Deformation

While the clinical and practical definition of the cancer is morphological, most cancer researchers believe, in spite of opposition,[19] that cancer is the outcome of DNA-mutational events.[20] The DNA-centered view of cancer etiology begins with the discovery that cancer cells carry chromosomal imbalance,[18] that chromosomes carry our heritable material,[21] that DNA therein is the molecule of heredity,[22] and that somatic DNA changes occur in and modulate the behavior of cancer cells.[23,24] It is hard to strictly apply Koch's postulates to the etiology of cancer; while organisms with inherited

oncogenic mutations often develop into cancer prone individuals, the mere viability of these mutants suggests that cancer is a complex multigenic syndrome. Single oncogene-transformed cells still require additional changes in order to exhibit the phenotype of full blown cancer.[25,26] Correlating with this, the majority of cells from premalignant human tissues already harbor multiple mutations[27,28] in that precursor state. Nevertheless, in a broader sense the DNA-centered view of cancer fulfils all Koch's postulates. Mutations found in cancer have been successfully isolated from a diseased organism,[24,29,30] have been shown to cause disease when introduced into a healthy organism,[31,32] and usually the sustainable presence of these mutations is necessary for maintenance of the disease state.[33,34] Thus, with some exceptions, re-deriving the mutation from the disease state is possible at any stage of the disease. The phenotype of a cancer cell involves multiple incremental changes[35] that accumulate in an escalating manner through extensive in vivo selection[25,36,37] and evolutionary dynamics.[38-40] Furthermore, the one-gene-one-function paradigm is systematically substituted with models where multiple gene products regulate a single phenotype, and single hits in any of those independent loci can give rise to the same outcome. Consequently, cancer causing mutations, from an etiological point of view, may be better categorized into pathways. If so, then even the first of Koch's postulates, i.e., that the oncogenic mutations must be found in all individuals suffering from the disease is fulfilled if you collate them into pathway groups. Indeed this is the case for canonical pathways, such as *RAS* and *PI3K*, where any given mutation is present in an average of 5% of the patients, and yet those pathways are deregulated in almost all cases.[26,41] A bigger discrepancy with Koch's postulates is the finding that many premalignant conditions carry such mutations, somehow without the full blown disease.[42-45] Extrinsic control of tumorigenesis and progression, which likely affect the genomic integrity indirectly via the selective pressure that premalignant cells are exposed to could therefore demark the premalignant to malignant transition.[19,46,47]

Cellular Deformation

The first notion of stromal control of cancer comes from the microscopic observation of Virchow that there is a strong association between morphological features of wounded tissue and inflammation and cancer (elevated levels of infiltrating inflammatory and immune cells).[48,49] Inflammation is also associated with an elevated risk of cancer.[49-52] In addition, by examining more than 900 autopsy records of patients with different primary tumors, Paget documented a non-random pattern of metastasis to visceral organs and was struck by the discrepancy between the relative blood supply and the frequency of metastases in certain organs, such as breast and prostate cancer spread to bones. This lead him to suggest what is now termed the "seed and soil" hypothesis, which assigns a role for both cancer and stromal cells in the establishment of distant metastasis, and consequently organ specific metastatic destiny preference.[53,54] In 1951, it was shown that skin irritation by carcinogen increased the efficiency of carcinogen-unexposed epithelial cell transformation.[55] Even in the context of cells expressing an activated oncogene, tumor formation still depended on wounding.[56,57] This suggested that carcinogenesis is reliant on higher order cell-cell interactions rather than on a simple cell autonomous DNA damage phenomena as suggested by Ames and colleagues.[58]

Integrating the Two Levels of Deformation in Cancer

Normal solid tissue is composed of multiple cell lineages, such as endothelial cells which constitute blood vessel walls, epithelial cells that make up body surfaces and provide glandular functions, and fibroblasts which comprise and direct the maintenance of connective tissue and the extracellular matrix. Between these major cell lineages, there is a dense protein barrier called basement membrane. To ensure that the basement membrane is properly positioned at the interface, heterotypic interactions between those cell lineages induce the mutual deposition of basement membrane components, laminins or collagens, by the epithelial or fibroblast cells, respectively. This barrier not only demarks the location of cells according to lineage commitment, but also plays a critical role in coordinating the functions, life span and behavior of the cells mainly through molecular attachment. As a result of this symbiotic mutual dependence of metazoan cells, the overall function of the organism depends on proper ratios and relative positioning of different cell types in the space of tissues. This remarkably complex tissue structure is achieved by a coordinate choreography, during which cells propagate and acquire identity concomitantly in response to their tissue location (Spemann-Mangold organizer effect as paradigm).[59-61] Perturbation to this morphological homeostasis, and the basement membrane in particular, either via mechanical injury or enzymatic degradation, induces a response generally termed as wound healing or inflammation. The desired outcome of this homeostatic response is the recovery of proper tissue structure and function. A malignant cell that invades and destroys this barrier violates this vital tissue architecture and morphological equilibrium and elicits a perpetual wound healing response in the cancer microenvironment.[62] In the context of malignancy, the wound healing response turns the invaded stroma from harmless boundary into an active tumor promoter.

Evolutionary Context for Cancer Promotion by Spontaneous Inflammatory Reaction

"Everywhere in nature we observe adaptations to the finest degree one can think of" (Schroedinger, 1998). It therefore seems counterintuitive that an unaltered healthy stroma would respond to the cancer in a manner that ameliorates the pathology and become an accomplice by spontaneous response, without a change in the stromal cells themselves. Yet, spontaneous cross talk between epithelial and stromal cells induces the expression of genes in both the stroma and cancer cells.[63-71] These genes include classical cancer stroma markers that reportedly may promote oncogenic potential of adjacent epithelia.[2,3,72-74] This is possibly due to the late presentation with carcinoma disease in human life span. Diseases that present in individuals at post reproductive age, are not expected to be selected against in human evolution.[75] By contrast, inflammation, which is an acute response to infection provides evolutionary advantage at reproductive age. Since recovery of the epithelial cell function is critical to wound healing, inflammation activates proto-oncogenes,[76] increases genomic instability, via oxidative radicals[52,77] and protects oncogene-transformed epithelial cells from apoptosis.[50,51,78] Considering the microevolution of cancer cells via somatic alterations, at the rate of somatic mutations observed in normal cells, it is difficult to envisage how cancer cells get to accumulate their typical havoc genome damage. It therefore follows that events

early in premalignant conditions[79] lead to an intrinsic increase in mutation rate, as well as loss of mechanisms that monitor genomic integrity and control the appropriate cellular response, such as DNA repair or cell death. Since inflammation accelerates almost all of the milestones of cancer progression, it follows that chronic inflammation is linked with increased risk of a few different cancer types. We consider the CAFs as part of these cancer microenvironment changes that occur in tissue lesions and serve as precursors for malignant disease. Several hypotheses have been presented for the origin of these altered cells, including standard connective tissue acute phase and stress response,[55,80,81] and fibroblast senescence,[82-85] reciprocal interactions with the cancer cells,[5,20,86-90] fibroblast specific somatic mutations,[91-95] differentiation precursors and infiltrating mesenchymal stem cell.[96,97]

Connective Tissue Acute Phase and Stress Response Model of CAFs

The first investigation of the role of altered stroma in cancer etiology was reported as early as 1951 where transplanted carcinogen (methylachollantrene)-treated skin mesenchymal cells were shown to induce an increased incidence of skin carcinoma. While these early experiments did not have methodologies to exclude the possibility that the cancers arose from contaminating epithelial cells, they nevertheless raised the compelling hypothesis that carcinogens affect tumor stroma, which then plays an initiator role in cancer etiology. More recently, this experiment was reproduced in rats for breast cancer,[81] however, again, the data lacks definitive proof that the malignancy is not a product of direct mutagenesis of epithelial cells contaminating the stromal adaptive transfer. It is also not clear if the cancer promotion was due to carcinogen induced somatic mutations or simply stress-related alterations in gene expression.[80,98,99]

The Fibroblast Senescence Model of CAFs

One of the prime barriers to oncogenic transformation is the limited license to proliferate in vitro that differentiated somatic cells exhibit, which means that by enlarge, elevated proliferation is unsustainable.[100-105] Cancer usurps this barrier by various intracellular mechanisms, but on the level of cancer microenvironment, senescence may also promote cancer.[106-108] The linear increase in cancer incidence with age fits the model of cumulative somatic mutations for cancer etiology[109-112] but other contributions of age are possible. In particular, age is correlated with generalized chronic increase in tissue inflammation.[49,50,85,107,113,114] Since senescent fibroblasts spontaneously express a host of inflammatory cytokines linked with cancer promotion[85] it has been proposed that normal fibroblasts of aging individuals play an initiating role in cancer etiology through an inherent CAF phenotype.[114] The majority of reports for CAFs however record that CAFs promote cancer to a greater extent than fibroblasts derived from distant tissue within the same patient, suggesting that CAFs arise from further biological events. Additionally, expression profiles of senescent fibroblasts partially, but not completely phenocopy the expression signatures of CAFs. Nevertheless, since proliferation accelerates senescence, it is possible that moderate increase in local mitogenic signals to the fibroblasts within cancer microenvironment (see next model), contribute to specific accumulation of senescent fibroblasts within cancer microenvironment beyond the normal tissues of the patient.

The Reciprocal Interactions Model of CAFs

In the cancer epithelial cell-centered model for carcinogenesis, CAFs are merely an inevitable response to the cancer causing mutations and are fundamentally no different from normal fibroblasts (as part of the inflammatory reaction described above).[115-118] The fibroblast response is hardwired in the genome as part of the cancer's resemblance to a chronic wound, aiming at support of epithelial cell survival and expansion.[119-128] In addition to parsimony, this hypothesis offers clear predictions to scientifically test against corresponding null hypotheses; (1) That co-culture of cancer cells with normal fibroblasts will induce expression of CAF-specific genes in the fibroblasts,[63-71] (2) that wounded fibroblasts should promote cancer in a way that is indistinguishable from CAFs,[129] and (3) that normal fibroblasts can transform into CAFs via co-cultivation with cancer cells in vivo for extended period of time (our unpublished work does not provide evidence for this prediction). Gene expression profiling of tumor-stromal interactions between co-cultured cancer cells and stromal fibroblasts have previously been performed for cancer cells with the corresponding organ-specific fibroblasts.[63-71] Many of the genes shown to be activated in these co-cultures are known markers of CAFs in vivo, such as MMP1, MMP3, collagens, TNC, etc. Evidence that this reciprocal interaction promotes cancer includes the anti-cancer effect of Imatinib, on carcinoma animal models. It was shown that inhibition of the PDGFRB in cancer stroma leads to attenuated bFGF signaling, and consequent attenuation of the carcinoma.[130] However, many of the genes that are elevated in CAFs do not undergo a change of expression in co-cultures. It is possible that some other cells in the tumor microenvironment and missing in the co-cultures, such as tumor associated macrophages, play a key role in regulating the phenotype of CAFs. Alternatively, some other aspect of the CAF-origin is not recapitulated by co-culture experiments.

The Mutational Model of CAFs

The impressive progress in the identification and characterization of tumor-causing mutations in oncogenes or tumor suppressor genes has in a sense indoctrinated our thinking about the underlying molecular basis of alterations in cell behavior.[26,35,131] Following the success with genome analysis of the cancer cell itself, it was only natural to use the same hypotheses for the exploration of all aspects of cancer, including the cancer microenvironment. Molecular genetic studies in breast cancer have reported somatic mutations in *TP53* and *PTEN* as well as gene copy number alteration at other loci in adjacent stroma[91,93,132] suggesting that much of the tumor promoting activity of stromal cells may be mutation based. The co-existence of mutations in two (or more) cell lineages, was initially claimed to be the product of sequential mutagenesis, where the oncogenic mutations occurred in the cancer cell first, and then in the consequent host infiltrate, as an inevitable outcome.[20] It was also suggested that multiple cell lineages concomitantly incur somatic mutations that favored cancer promoting symbiotic relationships between the cancer cell and the adjacent supporting connective tissue.[99] However, this concept is still contentious.[133] Considering the potential increased mutation rate in inflamed microenvironment, it is possible that the resident stromal cells could accumulate a random set of mutations. On the other hand, the classical working hypotheses on carcinogenesis assumes the mutation rate is affected by overall rate of proliferation,

which would be orders of magnitude lower in the stromal cells compared to the cancer cells. It was nevertheless exciting to see that somatic alterations were consistently observed at a high frequency (>30%) in tumor juxtaposed fibroblasts suggesting that these were the underlying molecular basis for the sustained cancer promoting attributes of CAFs.[91,93] Unfortunately, technical aspects of this body of work raised serious doubt as to whether these apparently frequent somatic mutations were genuine.[134] Our own studies have revealed only a single loss of heterozygosity event on chromosome 22 in one CAF population among 35 breast and ovarian cancers. Our data and the consensus of molecular genetic studies of CAFs where technical artifacts were avoided is that somatic alterations in clonal populations of CAFs are at best exceedingly rare.[9,10]

Hypothetically, the idea of co-evolution of two cell lineages in the body that carry independent somatic mutations is not implausible. An altered fibroblast that somehow entices the neighboring epithelia to secrete a support signal for other fibroblasts would be expected to consequently expand further. The altered fibroblast might propagate more rapidly than distant normal fibroblast counterparts since it is the source of the supporting environment and the effect might be expected to be much localized. However, in such scenario, unaltered fibroblasts immediately adjacent to this altered fibroblast are expected to expand at a similar rate in a manner reminiscent to satellite bacterial colonies that emerge in selective bacterial culture if the ampicillin selection was extended so long that the secreted β-lactamase fully eliminated the ampicillin in the vicinity of a resistant colony. This model predicts that if CAF mutations existed they would generate clonal expansion in the midst of unaltered bystander normal fibroblasts and they would not reach homogeneity of mutant cells. This means that even if a mutant fibroblast that promotes cancer was to benefit from this mutation directly, it might not be detectable with current technologies. If this co-evolution model of CAF mutations is correct, one would still expect to observe evidence for fibroblast proliferation which would be needed to drive the clonal expansion. However, Ki67 and PCNA staining of tumor sections invariably failed to detect proliferating fibroblasts. Similarly, in instances where immunohistochemistry is capable of detecting mutant proteins, such as p53, the signal is invariably centered on the cancer cells. Of course, speckled signal is sometimes observed for the stroma, but not necessarily above background. Overall, any model which incorporates somatic mutations in CAFs is not supported by empirical data and in our view is not a tenable explanation for the CAF phenotype.

Differentiation Intermediates and Mesenchymal Precursors Model of CAFs

The comparison between cancer and wounds[62] is based on the fact that both tissue regeneration and carcinogenesis involve cell proliferation, survival and migration that are controlled by growth factors and cytokines as well as inflammatory and angiogenic signals. In particular, tissue injury leads to acute recruitment of immune cell infiltrates, which are early markers of basement membrane breakdown, followed by more sustainable fibrosis.[135,136] Whereas it is possible that this fibrosis results from responses in local fibroblasts, mesenchymal precursors are also known to be recruited to injured tissue,[137] as well as cancer.[138] Most compellingly, knee aspirate-derived human mesenchymal stem cells were shown to support not only primary cancer growth,[97] but most importantly overall breast cancer metastasis. Unfortunately, these experiments were not performed side-by-side with CAFs and normal fibroblasts from the same individuals. Since the activity of precursor cells is defined by in vitro colony forming capacity, it is hard to predict the expected result in the case that these cells are indeed the source of CAFs in cancer tissue. The simple prediction would be that a large fraction of the fibroblastic cell population in tumors would be progeny of mesenchymal precursor cells that migrated from an external body pool. While some evidence suggest this indeed is the case,[138] using βGal$^+$ ROSA 26 bone marrow—derived mesenchymal cells we only observed small numbers of such progeny in tumor cross sections (manuscript in preparation). Precursor cells may convey tissue regeneration by coordinating the proliferation and migration of other cells, and play a critical role in the process, without contributing a large fraction of the ultimate cell numbers. In fact, in the case of tumor vasculature it was observed that endothelial precursor cells only produce a small fraction of progeny cells that are recognized within tumor vasculature, yet their infiltration into tumors is critical for the overall formation of tumor vasculature.[139] Whilst this is a plausible model, there is no evidence for this model to date. Another source of differentiation intermediates potentially contributing to CAF activity may be from tissue pericytes. These peri-vascular cells share a large number of cell markers with CAFs including PDGFRB, Thy-1 and NG2. In tumors however, these markers are not restricted to the peri-vascular position as they are in normal tissues.[140] Evidence supporting the link between pericytes and CAF-like cancer support comes from analysis of the effect of STI-571 in mouse carcinoma models.[130] While these models are compelling, the ultimate validation would come from animal model experiments where adaptive transfer of mesenchymal precursor, either from the bone or normal tissue, could be assayed for the capacity to promote cancer growth as compared to original CAFs.

Concluding Remarks

It is important to note that the models described in this review are not mutually exclusive, both across different patients, as well as across different fibroblastic cells in any given tissue since cell marker studies indicate that fibroblasts are quite heterogeneous.[140] The heterogeneity of the tissue fibroblasts is critical, since the biological activity that CAFs convey onto to cancer has not been purified to homogeneity, nor is there an assessment of the specific activity for these assays, i.e., how many of the fibroblasts deliver the functional effect, in the background of irrelevant fibroblast cells. Thus, either of those populations could be responsible for the observed support of cancer, in addition to expressing distinct sets of gene products. This also means that the tumor stromal cells that promote cancer in the animal assays for CAFs may in fact carry a unique set of somatic mutations, which were obscured by the diploid genome of the majority of the stromal fibroblasts, which may be viewed as innocent bystanders. However, this possibility cannot explain the previous publications claiming accumulation of mutations in the bulk carcinoma fibroblasts, nor can this possibility be addressed until the cells that promote cancer are further purified to homogeneity.

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