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The detached pericyte hypothesis: A novel explanation for many puzzling aspects of tumorigenesis

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Abstract

The standard, generally accepted, theory of tumorigenesis, says that tumors arise from a succession of driver mutations and clonal expansions. However, this standard theory has difficulty explaining many puzzling phenomena in tumorigenesis including (i) foreign-body tumorigenesis, (ii) transgenic mouse tumors that lack the inducing mutation, the synergistic effects of various carcinogens, (iii) cancer resistance in naked mole rats, (iv) different cancer rates for hereditary conditions with similar DNA repair defects, (v) carcinogenic exposure of stromal cells leading to tumors in epithelial cells, and (vi) the roles of BRCA1 mutations, obesity, asbestos, schistosomiasis, viruses, and smoking in carcinogenesis. The proposed detached pericyte hypothesis provides novel explanations for these phenomena. The detached pericyte hypothesis postulates the following events. A carcinogen or chronic inflammation causes pericytes to detach from blood cell walls, either directly through vascular injury or indirectly through fibrosis followed by collagen contraction and obliteration of capillaries. Some detached pericytes form myofibroblasts which increase fibrosis and alter the extracellular matrix. Other detached pericytes develop into mesenchymal stem cells that adhere to the altered extracellular matrix of the the fibrosis. The altered extracellular matrix disrupts regulatory controls, causing the adjacent mesenchymal stem cell to develop into tumors. Various lines of evidence support the detached pericyte hypothesis. Further investigations into the detached pericyte hypothesis, ideally in the framework of multiple working hypotheses, would likely accelerate progress in cancer research and prevention.

Keywords: carcinogenesis; fibrosis; inflammation; mesenchymal stem cell; pericyte

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1. Introduction

The physicist Lisa Randall wrote, "we often fail to notice things that we are not expecting" (Randall 2015). Randall's sentence could readily apply to cancer research. The standard, generally accepted, theory of carcinogenesis says that cancer arises from a succession of driver mutations and clonal expansions (Vogelstein et al 2013). When researchers focus on the standard theory of carcinogenesis they often overlook unexpected and puzzling experimental and observational phenomena (Baker 2015). The proposed detached pericyte hypothesis provides a novel explanation for many of these puzzling phenomena.

The detached pericyte hypothesis is closely related to the tissue organization field theory of cancer (Sonnenschein and Soto, 1999, Soto and Sonnenschein 2011, Sonnenschein and Soto 2016) with respect to the important role of disrupted tissue regulatory control. It also overlaps hypotheses of tumorigenesis involving the role of fibrosis (Brücher and Jamall 2014) and tissue mechanics (Ingber 2008, Bizzarri and Cucina, 2014).

Pericytes, which are elongated cells attached to blood vessel walls, regulate blood flow and support vessel remodeling. Recently pericytes have generated considerable interest because of their multipotent differentiation capacity (Ribeiro and Okamoto 2015).

Until now, there has been very little discussion concerning the role of pericytes in the initiation of tumors.

2. Hypothesis

The detached pericyte hypothesis of tumorigenesis consists of five interrelated parts:

1. A carcinogen or chronic inflammation (which may be caused by the carcinogen) causes pericytes to detach from blood vessel walls either directly through vascular damage or indirectly through fibrosis followed by collagen contraction and obliteration of capillaries.
2. Some detached pericytes form myofibroblasts, which lead to fibrosis and stiffening of the extracellular matrix.
3. Some detached pericytes develop into mesenchymal stem cells.
4. Some of these mesenchymal stem cells adhere to the fibrotic tissue.
5. The abnormal stiffness of the extracellular matrix disrupts regulatory controls causing the adhered mesenchymal stem cells to develop into tumors (sarcomas or carcinomas).

As noted by Prehn (1994), "no cancer exhibits any trait which cannot be found in some normal tissue as the expression of normal genomic activity." The disruption of regulatory controls in the detached pericyte hypothesis could explain all the traits associated with cancer.

3. Motivation

Motivation for the detached pericyte hypothesis comes from foreign-body tumorigenesis, which was a major topic of cancer research in the 1960s and 1970s (Brand, Johnson, and Buoen 1976). Some cancer researchers may view foreign body tumorigenesis as an anomaly unrelated to the development of most tumors. The alternative view here is that foreign-body tumorigenesis is a window into tumor development. Two noteworthy results are as follows. First, subcutaneous nonporous implants in mice yielded sarcomas, while implants in powdered form yielded no sarcomas, a result that did not depend on the composition of the implant (Brand, Johnson, and Buoen 1976). Second, filter implants with small pore sizes induced fibroid capsules and sarcomas, while filter implants with large pore sizes induced no fibroid capsules and no sarcomas (Karp et al 1973).

There was a large effort to identify the progenitor cell in foreign body tumorigenesis. Based on results from transplantation experiments, investigators ruled out the bone marrow as a source for the progenitor cell (Barnes, Evans, and Loutit 1971). Next, investigators considered the most conspicuous cells involved in the local reaction to the foreign-body, namely monocytes, macrophages, and fibroblasts (Brand et al 1975). Because the implants induced a variety of sarcoma types, as would be consistent with a pluripotential progenitor cell, and because of a resemblance between some subcellular features and pericyte, Johnson et al (1973) hypothesized that the cancer progenitor cell in these experiments was, in fact, a pericyte.

To investigate the development of the progenitor cells, Moizhes and Prigoshina (1973) and Brand, Buoen, and Brand (1971) subcutaneously inserted a nonporous disk into mice, removed the resulting fibroid capsule, inserted a new non-porous disk, and transplanted the combined donor capsule and new disk to a recipient mouse that had a different karyotype from that of the donor mouse. Because the sarcomas in the recipient mice had the same karyotype as the donor mouse, they concluded that the progenitor cell arose in or near the fibroid capsule of the donor mouse. When they transplanted the fibroid capsule without the disk to recipient mouse, they rarely found sarcomas in the recipient mouse. Thus, the adherence of the progenitor cells to the implant occurs after the formation of the fibroid capsule.

Based on the results of the implant transplantation experiments and the association of fibroid capsules with tumorigenesis in the Millipore filter experiments, Brand, Buoen, and Brand (1971) hypothesized the following two-stage process for foreign-body tumorigenesis. First, the implant creates a fibroid capsule. As the collagen in the fibroid capsule contracts, it compresses and obliterates capillaries, causing pericytes to disconnect from the blood vessel wall. Second, some disconnected pericytes adhere to the implant. The implant disrupts tissue specific controls, causing the adhered pericytes to develop into sarcomas.

In a few cases, removal of the implant led to both a scar and a sarcoma in the fibroid capsule. Brand et al (1975) hypothesized that the scar functioned like a foreign-body implant, with the detached pericyte adhering to the scar and developing into a sarcoma – a key motivation for detached pericyte hypothesis.

4. Support for the hypothesis

The detached perictye hypothesis says that a carcinogen or chronic inflammation detaches pericytes that (1) induce fibrosis and alter the extracellular matrix and (2) develop into mesenchymal stem cells that adhere to the altered extracellular matrix and develop into tumors (carcinomas or sarcomas). Various lines of evidence support detached pericyte hypothesis.

4.1. Evidence that a carcinogen or chronic inflammation detaches pericytes

Various studies show that vascular injury, which could arise from the carcinogen or chronic inflammation, detaches pericyte in the kidneys, lung, and spinal cord (Marrache et al 2008, Göritz et al 2011, Birbrair et al 2014, Schrimpf et al 2014).

4.2 Evidence that some detached pericytes develop into myofibroblasts, which lead to fibrosis

Fate tracing experiments involving the kidney and liver show that detached pericytes can form myofibroblasts (Humphreys et al 2010, Mederacke et al 2013). Also, liver injury transforms pericytes into myofibroblasts (Rockey, Weymouth, and Shi, 2013). Myofibroblasts play an important role in fibrosis and the remodelling of the extracellular matrix (Tomasek et al 2002, Wyn 2008). Many studies indicate a link between inflammation and fibrosis (Lee and Kalluri 2010) and between injury and fibrosis (Hutchinson, Fligny, and Duffield 2013).

4.3. Evidence that some detached pericytes develop into mesenchymal stem cells

Many studies have demonstrated a perivascular origin of mesenchymal stem cells in various human organs (Crisan et al 2008). Examples include differentiation of pericytes into chondrocytes and adipocytes (Farrington et al 2004), skeletal muscle (Cappellari and Cossu 2013), and odontoblasts (Feng et al 2011).

4.4. Evidence linking mesenchymal stem cells to the development and repair of epithelial cells

Various studies show that mesenchymal stem cells play a role in the development or repair of epithelial cells, suggesting the potential for mesenchymal stem cells to develop into carcinomas. Mesenchymal stem cells can differentiate into epithelial cells (Phinney and Prockop 2007), including alveolar type I epithelial cells (Kotten et al 2001), retinal pigment epithelial cells (Arnhold et al 2007), skin epithelial cells (Nakagawa et al 2005), sebaceous duct cells (Fu et al 2006), and tubular epithelial cells in kidney (Morigi et al 2004, Herrera et al 2004). Also, mesenchymal stem cells can promote the renewal of epidermal tissue from non-stem cells (Pageuet-Fifield et al 2009), induce epithelial proliferation in the inflamed stomach (Donelly et al 2014), and generate neuroendocrine Leydig cells (Davidoff et al 2009). Pericyte accumulation in the airway wall may contribute to airway remodeling in chronic asthma (Johnson et al 2015). Bone marrow derived mesenchymal stem cells are associated with repair of lung, pancreas, liver, and intestine (Kotton et al 2001, Li and Ikehara 2013).

4.5. Evidence linking mesenchymal stem cells to sarcomas

Various studies show that mesenchymal stem cells are likely progenitors of sarcomas (Matushansky et al 2007, Xiao et al 2013, Sato, Tang, Wei et al 2016). Mice with subcutaneously implanted microbeads with attached mesenchymal stem cells developed sarcomas while controls with implanted microbeads and no attached mesenchymal stem cells did not develop sarcomas (Boone and Jacobs,1976).

4.6. Evidence linking mesenchymal stem cells to carcinomas

Mesenchymal stem cells have been linked to epithelial cancer. Adipose mesenchymal stem cells, which originate from perivascular cells (Cai et al 2011), have been linked to tumor initiation in breast and colon cells (Wei et al 2015). Bone marrow derived mesenchymal stem cells, which are thought to be pericytes (Cai et al 2009), have been implicated in mouse gastric cancer (Houghton et al 2004). A recipient of a bone marrow transplant developed adenocarcinoma of the esophagus from bone-marrow derived donor cells (Hutchinson et al 2011). A recipient of a hematopoietic stem cell transplant developed gastric adenocarcinoma from the donor cells (Arai et al 2006). Lastly, a kidney transplant recipient developed skin carcinoma linked to donor cells, that were likely mesenchymal stem cells (Aractingi et al 2005). Although almost all foreign-body induced neoplasms are sarcomas, some implants in the lumen of epithelial-lined organs have induced carcinomas (Brand, Johnson, and Buoen 1976).

4.7. Evidence supporting the role of the extracellular matrix in tissue development

The extracellular matrix affects the development of normal tissue, a likely prerequisite to the role of altered extracellular matrix in tumorigenesis. Mesenchymal stems cells grown on polymer gels express neuronal, muscle, and bone proteins when the stiffness of the gels resembled that of the brain, muscle, and bone, respectively (Lu, Weaver, and Werb, 2012). In vivo experiments showed that mammary extracellular matrix directs the differentiation of testicular and embryonic stems cells to form mammary glands (Bruno et al 2017). Human mesenchymal stem cells cultured on a collagen gel differentiated into epithelial-like cells (Takebayashi et al 2013). The transplantation of fetal salivary mesenchymal cells into adult mammary glands yielded outgrowths resembling salivary glands (Sakakura, Sakagami, and Nishisuka 1981).

4.8. Evidence supporting the role of the extracellular matrix in tumorigenesis

Various studies show that the stiffness of the extracellular matrix affects the development of cancer cells. The optimal stiffness of a matrix for growing cancer cells depends on the type of cancer (Jabbari et al 2015). Increased collagen density promotes mouse mammary tumors (Provenzano et al 2008). The degree to which a chemical carcinogen changes collagen and elastic fibers is associated with the potency of the carcinogen (Orr 1958). A highly rigid stromal phenotype is linked to pancreatic ductal adenocarcinoma (Laklai et al 2016). A stiff extracellular matrix induces a malignant phenotype in normal mammary cells (Chaudhuri et al 2014).

4.9 Evidence linking fibrosis and tumors

Many observational studies found an association between fibrosis and precancerous lesions or cancer. Examples include radiation-induced cancer (Martin, Lefaix, and Delanian 2000), Barret's esophagus (Abraham et al 2007), oral pre-cancer (Bag et al 2013), hyperplasia in the pancreas (Detlefsen 2005), asbestos-related cancer (Davis and Cowie 1990), and liver cancer (Yin et al 2013). A risk factor for basal cell carcinoma is the presence of scar tissue (Ozyazgan and Kontaçs 2004). Pulmonary scarring increases lung cancer risk in the same lung as where the scarring occurred, but not in the contralateral lung (Yu et al 2008). Zinc deficiency increases both fibrosis (Navarro et al 1994) and cancer incidence (Abnet et al 2005). Molecular iodine inhibits fibrosis in mammary glands (Eskin et al 1995) and prevents cancer promotion (Garcia-Solis et al 2005).

4.10. Evidence linking pericytes and tumors

Evidence supporting the detached pericyte hypothesis also comes from a recent study to characterize the molecular events during melanoma initiation (Kaufman et al 2016). Visualization through live imaging showed that activated neural crest cells are a key event in melanoma initiation from a field of cancer-prone melanocytes. Because pericytes can arise from neural crest cells (Armulik, Genové, and Betsholtz 2011), these results are consistent with pericytes playing a key role in tumor initiation.

5. Puzzling experimental results

The detached pericyte hypothesis suggests novel explanation for various experimental results that are puzzling under the standard theory of carcinogenesis.

5.1. *Myc* inactivation and tumor regression

In what has been called a landmark paper, Shachaf et al (2004) discovered that after turning on the *Myc* gene to induce liver cancer, turning off the *Myc* gene caused tumor cells to differentiate into normal cells. Overexpression of *c-myc* in mouse hepatocytes increases proliferation of pericytes and collagen deposition (Nevzorova et al, 2013). The detached pericyte hypothesis suggests that (i) the activated *Myc* gene detaches pericytes and alters the extracellular matrix to which the detached pericytes adhere and (ii) the inactivated *Myc* gene allows the extracellular matrix to return to normal, which reinstates the normal regulatory signals and leads to tumor regression.

5.2. *RBP-J_K* deleted transgenic mice

Transgenic mice with deletion of the *CSL/RBP-J_K* gene developed multifocal keratinocyte tumors in which tumor cells showed no deletion of the *RBP-J_K* gene (nor mutations in *p53* or *Ha-*, *Ki-*, or *N- ras* genes) (Hu et al 2012), a puzzling result if deletion of the *RBP-J_K* gene is a driver mutation. The transgenic mice had reduced elastic fibers and expressed Tenascin-C in the dermis (Hu et al 2012). Tenascin-C promotes the migration of pericytes in the liver (Ma et al 2016). The de-

tached pericyte hypothesis suggests that the deletion of the *RBP-J_K* gene increases pericyte detachment and migration (by increasing Tenascin C) and these detached pericytes adhere to the altered extracellular matrix (indicated by the change in elastic fibers) leading to tumors without the deletion of the *RBP-J_K* gene.

5.3. *Dicer 1* deleted transgenic mice

Transgenic mice with deletion of the *Dicer1* gene in stromal bone progenitor cells developed acute myelogenous leukemia without *Dicer1* deletions (Raaijmakers et al 2010), a puzzling result if deletion of the *Dicer1* gene is a driver mutation. Mutations in *Dicer1* are associated with increases in collagen (Yu et al 2014). The detached pericyte hypothesis suggests that the *Dicer1* deletion increases collagen that subsequently contracts, obliterates capillaries, and detaches pericytes, which then adhere to collagen, leading to tumors without the *Dicer1* deletion.

5.4. Radiation and implants

Experiments in mice involving radiation and perforated polymer film implants yielded the following tumor incidence rates: 24% for the film implant alone, 4% for gamma radiation alone, and 52% for the synergistic effect of gamma radiation followed by the film implant (Moizhess and Vasiliev 1989). Radiation leads to the formation of fibrous tissue (Rodemann and Bamberg 1995). The detached pericyte hypothesis suggests that radiation-induced fibrosis leads to detached pericytes which adhere to the fibrosis and the implant, yielding a synergistic effect on tumorigenesis.

5.5. Ethylnitrosurea and implants

Experiments in mice involving the chemical carcinogen ethylnitrosurea and perforated film implants yielded the following tumor incidence rates: 16% for the film implant alone, 0% with ethylnitrosurea exposure alone, and 50% for the synergistic combination of ethylnitrosurea exposure followed by the film implant (Moizhess and Vasiliev 1989). Precursors of ethylnitrosurea lead to unusually thin capillaries that sometimes disintegrate (Rustia 1974), suggesting the possibility that ethylnitrosurea causes pericytes to detach from the blood cell wall. The detached pericyte hypothesis suggests that ethylnitrosurea detaches pericytes which adhere to the film implant, yielding a synergistic effect on tumorigenesis.

5.6. DMBA and radiation

Experiments in hamster cheek pouch epithelium involving Dimethylbenz(a)anthracene (DMBA) and radiation yielded the following tumor incidence rates: 0% for radiation alone, 53% DBMA alone, and 75% for the synergistic effect of DBMA and radiation (Lurie et al 1983). DMBA increases vascular permeability (Lurie et al 1985) and vascular permeability detaches pericytes (Armulik, Genové, and Betsholtz 2011). The detached pericyte hypothesis suggests that DMBA detaches pericytes which adhere to the radiation-induced fibrosis, yielding a synergistic effect on tumorigenesis.

5.7. DMBA and croton oil

In a classic tumor initiation and promotion experiment, exposure of mice to DMBA followed by the application of croton oil yielded an incidence of skin tumors that was much higher than with either DBMA or croton oil alone (Appleton et al 1992). Croton oil is associated with the granulation of tissue, which can lead to scar tissue, and increased production of myofibroblasts (Appleton et al 1992). Reducing the number of fibroblasts after the administration of the active ingredient in croton oil substantially reduces the number of tumors (Zhang et al 2011). The detached pericyte hypothesis suggests that DMBA detaches pericytes (by increasing vascular permeability) and the detached pericytes adhere to scar tissue induced by croton oil, yielding a synergistic effect on tumorigenesis.

5.8. Stromal target of carcinogen

Maffini et al (2004) removed mouse mammary epithelial tissue adjacent to stromal fat pad tissue, exposed the stromal pad tissue to a carcinogen, inserted the unexposed mammary epithelial tissue next to the exposed stromal tissue, and observed a high incidence of epithelial cancers (that was not observed with the same protocol but with a non-carcinogen). The detached pericyte hypothesis suggests that the carcinogen induced fibrosis in the stroma, causing collagen contraction and the detachment of pericytes which adhered to the altered stromal extracellular matrix bordering the epithelial tissue. Supporting evidence comes from the link between changes in stromal fibroblasts and the growth of tumors in adjacent epithelial tissue (Bhowmick et al 2004).

5.9. Spontaneous regression

Administration of a carcinogens to mice for 3 exactly months yielded hepatic nodules which regressed, while administration for exactly 4 months led to persistence

of nodules and high cancer risk (Teebor and Becker 1971). The detached pericyte hypothesis suggests that the 4-month dose induced a permeant alteration of the extracellular matrix while a 3- month dose induced only a temporary alteration of the extracellular matrix.

5.10. Denervation experiments

The neurobiology of cancer is an emerging discipline (Boilly et al 2017). Denervation in the mouse stomach is associated with inhibition of Wnt signaling and reduced tumor incidence (Zhao et al 2004). Aberrant Wnt signaling is a driver of fibrogenesis (Enzo et al 2015). The detached pericyte hypothesis suggests that denervation reduces tumor incidence by reducing fibrosis via Wnt inhibition.

5.11. Non-genotoxic carcinogens

Non-genotoxic carcinogens induce cancer without altering DNA, chromosome number or structure (Hernández et al 2009). Many non-genotoxic carcinogens cause inflammation or fibrosis (Hernández et al 2009). The detached pericyte hypothesis suggests that many non-genotoxic carcinogens induce cancer by increasing fibrosis.

6. Puzzling observational results

The detached pericyte hypothesis suggests novel explanation for various observational results that are puzzling under the standard theory of carcinogenesis.

6.1. Age and latency effects

At a minimum, any hypothesis about tumorigenesis should explain the following two phenomena: increased cancer incidence with age (Elkahattouti, Hassan, and Gomez 2015) and a long latency between the time of carcinogenic exposure and the development of cancer (Armenian, 1987). The detached pericyte hypothesis suggests that increased cancer incidence with age is a consequence of increased fibrosis with age (Elkahattouti, Hassan, and Gomez 2015), and the long latency period in many cancers reflects the time needed for fibrosis to develop.

6.2. Cancer resistance in naked mole rat

A fascinating question in cancer biology is why the naked mole rat rarely develops cancer (Edrey et al 2011). Fibroblasts in the naked mole rate secrete a special form of the sugar molecule hyaluronan that has a molecular mass five times larger than hyaluronan in humans or mice (Tian et al 2013). Removing high-molecular mass hyaluronan via a genetic knockdown led to tumors, implying that high-molecular mass hyaluronan plays an important role in cancer resistance (Tian et al 2013). High-molecular mass hyaluronan dampens fibrosis (Toole 2004, Tolg, Telmer, and Turley 2014, Albeiroti S, Soroosh A, and de la Motte 2015). The detached pericyte hypothesis suggests that high molecular mass hyaluronan inhibits carcinogenesis by inhibiting fibrosis.

6.3. BRCA1 mutations and breast cancer

The major high-penetrance genetic susceptibility pathway to breast cancer involves mutations in *BRCA1* and *BRCA2* (Easton, Ford, and Bishop 1995, Baker 2016). *BRCA1* and *BRCA2* mutations are associated with dense breast tissue (Huo et al 2002). Dense breast tissue is associated with stromal fibrosis (Boyd et al 1998) and breast cancer (Vachon et al 2007). The detached pericyte hypothesis suggests that mutations in *BRCA1* and *BRCA2* increase the risk of developing breast cancer by increasing the density of breast tissue and hence increasing fibrosis.

6.4. Hereditary skin cancer

The hereditary conditions of Xeroderma pigmentosum (XP) and Cockayne Syndrome (CS) both involve defects in the DNA nucleotide excision repair that protects against sunlight DNA damage. Therefore, it is paradoxical that XP patients have a thousand-fold increase in susceptibility to skin cancer while CS patients have a normal skin cancer risk (Kraemer et al 2007). Actinic keratosis is a scaly patch on the skin that develops after years of exposure to the sun. It is associated with changes in the surrounding tissue (Pearse and Markes 1977) and strongly associated with the development of skin cancer (Fuchs and Marmur 2007). Although actinic keratosis has been observed in XP patients (Yarosh et al 2001), no cases of actinic keratosis were observed in a series of 140 CS patients (Nance and Berry 1992). The detached pericyte hypothesis suggests that the difference in cancer rates between XP and CS patients arises from different rates of actinic keratosis between XP and CS patients, where either the mechanical properties of actinic keratosis directly modify attached mesenchymal stem cells or the actinic keratosis is a marker for changes in stiffness of the extracellular matrix.

6.4. Obesity and cancer

There is growing evidence of a link between obesity and cancer (Lauby-Secretan et al 2016) but with considerable debate over the mechanism (de Pergola and Silvestris 2013). Obesity is associated with fibrosis (Marchesini et al 2008). The detached pericyte hypothesis suggests that obesity increases the rate of cancer by increasing the rate of fibrosis. Butyrate, an important metabolite in the colonic lumen that can be produced from dietary fiber (McIntyre, Gibson, and Young 1993), reduces the incidence of colon cancer (Sengupta, Muir, and Gibson 2006) and protects against diet-induced obesity (Chakraborti 2015). The detached pericyte hypothesis suggests that butyrate reduces colon cancer risk by reducing obesity.

6.5. Schistosomiasis and bladder cancer

Schistosomiasis is an infection caused by parasitic flatworms in fresh water in tropical regions. The flatworms penetrate the skin and migrate through the bloodstream to the bladder where they lay eggs which cause fibrosis (Fried, Reddy, Mayer 2011). Epidemiological evidence links schistosomiasis to bladder cancer (Palumbo 2007). The detached pericyte hypothesis suggests that schistosomiasis leads to bladder cancer via fibrosis of the bladder.

6.6. Asbestos and lung cancer

Epidemiological studies have linked asbestos exposure and cancer (Liddell and Hanley 1985), but the mechanism is not known (Barrett 1994). Asbestosis is a type of fibrosis occurring in the lungs exposed to asbestos. A prospective study of men employed in the manufacture of asbestos cement products found that the excess risk of lung cancer was restricted to men with evidence of asbestosis (Hughes and Weill 1991). The detached pericyte hypothesis suggests that asbestos leads to lung cancer via asbestosis.

6.7. Smoking and lung cancer

Although the link between smoking and lung cancer is well established, there is continued debate over the mechanism (Xue, Yang, and Seng 2014). Chronic obstructive pulmonary disease in smokers is associated with lung cancer (Papi et al 2004) and increased collagen forming scar tissue in the airways (Jeffrey 2004). Chemicals in cigarette smoke can diffuse through the lung epithelium to modify stromal fibroblasts (Salem, et al 2013). The detached pericyte hypothesis suggests that smoking increases the risk of lung cancer by modifying the stromal tissue to increase fibrosis.

6.8. Viruses and cancer

The link between viruses and human cancer is puzzling because there is no obvious molecular rule to determine if a virus is carcinogen, and there is no obvious explanation for the long latency period between exposure to the virus and incidence of cancer (Moore and Chang 2010). Viruses are associated with apoptosis (Roulston, Marcellus, and Branton 1999) and the dysregulation of apoptosis can lead to scarring and fibrosis (Grenhalgh 1998). Hepatitis B virus is associated with both liver fibrosis and liver cancer (Tsai and Chung 2010). The detached pericyte hypothesis suggests that viruses lead to cancer via apoptosis, which leads to scarring and fibrosis.

Another puzzling result is that chickens injected with Rous sarcoma virus develop tumors at the site of experimental wounds with over a 95% frequency (Dolberg et al 1985). In humans, basal cell carcinomas sometimes arise at the site of smallpox vaccinations (Rich, Shesol, and Horne 1980). The detached pericyte hypothesis suggests that wounding detaches pericytes and virus infections increase fibrosis, leading to a synergistic effect of wounding and virus infections on tumorigenesis.

7. Mutations

The detached pericyte hypothesis does not require mutations for tumorigenesis. However, under the detached pericyte hypothesis, mutations can arise as by-products of tumorigenesis (Prehn 1994) and can influence tumorigenesis via pathways to fibrosis.

7.1 Passenger mutations

There is extensive evidence that many mutations are “passengers” that do not contribute to tumorigenesis (Vogelstein et al 2013). For example, morphologically identical tumors in older patients have more mutations that in younger patients (Vogelstein et al 2013). Also, some benign conditions have higher levels of mutations than their malignant counterparts (Kato et al 2016).

The detached-pericyte hypothesis suggests that passenger mutations arise from a loss of regulatory controls to the mesenchymal stem cells that adhere to the

altered extracellular matrix. Supporting this view is the observation that as mesenchymal stem cells age, they induce p53 mutations (Li et al 2007).

7.2. Mutations in pathways to fibrosis

The detached pericyte hypothesis suggests that mutational pathways may influence carcinogenesis by their effect on fibrosis. At least four pathways regulate the transition from pericytes to myofibroblasts: Hedgehog, transforming growth factor- beta 1 (TGF-β1), platelet derived growth factor (PDGF), and connective tissue growth factor (CTGF) (Humphreys 2012). These pathways are associated with both cancer and fibrosis

The Hedgehog pathway has been implicated in tumor initiation (Hanna and Shevde 2016). It is also associated with lung fibrosis (Stewart et al 2003) and the transition of pericytes to fibroblasts in the liver (Choi et al 2009). Hedgehog signaling during pancreatic carcinogenesis is restricted to the stromal compartment (Tian et al 2009), suggesting its indirect role in carcinogenesis.

The misregulation of TGF-β pathway is linked to tumor development (Massagué 2008). TGF-β1 plays a critical role in fibrosis (Pohlers et al 2009) and tissue-level mechanics (O'Connor and Gomez 2014).

Increasing evidence indicates that dysregulation of PDGF signaling can influence cancer development (Farooqi and Siddik 2015). PDGF is implicated in renal fibrosis (Floege, Eitner, and Alpers 2008). The overactivation of TGF-β1 and PDGF pathways initiate the transition from pericytes to myofibroblasts in kidney fibrosis (Chen et al 2011, Wu et al 2013).

CTGF expression has been linked to tumor development and progression (Chu et al 2008). It is also associated with renal fibrosis (Van Nieuwenhoven et al 2005) and pericyte migration and adhesion (Abraham et al 2008).

Additional pathways may also be implicated in cancer via their role in fibrosis. The PI3K pathway is associated with early lung cancer development (Gustafson et al 2010) and plays a role in activation of pericytes in liver fibrosis (Son et al 2013). The *p53*, *KRAS*, and microRNA pathways, which are often associated with cancer (Li and Kowdely 2012), also play a role in fibrosis (Kodama et al 2011, Wang et al 2012, Jiang et al 2010). In mice with a *KRAS* mutation, pancreatic intraepithelial neoplasia is associated with pericyte activation (Lin et al 2016).

8. Implications

The detached pericyte hypothesis suggests new directions for research into better methods for primary cancer prevention and for the early detection of cancer that would hopefully trigger effective early intervention.

8.1. Cancer prevention

The detached pericyte hypothesis has important implications for cancer prevention. Because the detached pericyte hypothesis centers on fibrosis, searching for new anti-fibrotic agents may be a promising strategy for cancer prevention research. Two anti-fibrotic agents that have been investigated for the chemoprevention of cancer are aloe vera (Saini, Goyal, and Chaudhary 2010) and curcumin (Park et al 2013). In animal experiments, an extract from the aloe vera plant substantially reduced fibrosis (Salem, El-Azab and Faruk, 2014) and curcumin inhibited the development of fibrosis (Lee et al 2010). Another anti-fibrotic agent under consideration for cancer prevention is metformin (Quinn et al 2013). Metformin attenuates lung fibrosis (Sato,-Takaska,Yoshida et al 2016) and reduced the number of new adenomas or polyps in a randomized trial of patients with previous adenomas (Higurashi et al 2016). Anti-fibrotic agents that may be worth investigating for the chemoprevention of cancer are Mitomycin C, an anti-fibrotic used in ophthalmology without major side effects (Veen and Dikkers 2010), peptide 15-1, a small protein that promotes scar-less healing (Tolg et al 2012), and diabetes treatments (sitagliptin and vildagliptin) that inhibit enzymes linked to cutaneous scarring (Rinkevich et al 2015). A recent proposal to use hyaluronan signaling as a novel target for anti-fibrotic therapy (Klingberg, Hinz, and White 2013) is supported by the previous discussion concerning the role of hyaluronan in cancer resistance in the naked mole rat. Natural killer cells, which limit fibrosis by killing myofibroblasts (Fasbender et al 2016), could also play a role in chemoprevention. Another strategy is inhibition of core fucosylation to reduce fibrosis by modifying pathways from pericytes to myofibroblasts (Wang et al 2017).

8.2 Cancer early detection

The detached pericyte hypothesis has important implications for the early detection of cancer. Elastography, which measures the degree of fibrosis (Carstensen, Parker, and Lerner 2008) could potentially provide an early indication of cancer risk. Exosomes are vesicles

involved in intercellular communication that have been linked to fibrosis and pericytes (Yamamoto, Niida, and Azuma 2015). In mice with pancreatic cancer, the uptake of exosomes by the liver was associated with increased fibrosis and increased expression of macrophage migration inhibitory factor, a protein which showed promise in predicting cancer progression (Costa-Silva et al 2015). Thus, markers related to exosomes may have potential for the early detection of cancer.

9. Multiple working hypotheses

It is important to put the detached pericyte hypothesis into perspective as one of many hypotheses for tumorigenesis that should considered.

9.1. Theory of working hypotheses

Chamberlin (1890) discussed three methods to guide scientific inquiry: the ruling theory, the single working hypothesis, and multiple working hypotheses. A ruling theory is detrimental (unless it happens to be true) because it discourages investigations outside of its scope. Along these lines Chamberlin (1890) noted:

> there is an unconscious selection and magnifying of the phenomena that fall into harmony with the theory and support it, and an unconscious neglect of those that fail of coincidence.

James (1890) made a similar point,

> Round about the accredited and orderly facts of every science there ever floats a sort of dust-cloud of exceptional observations, of occurrences minute and irregular, and seldom met with, which it always proves less easy to attend to than to ignore…. When, moreover, as so often happens, the reports of them are vague and indirect, when they come as mere marvels and oddities rather than as things of serious moment, one neglects or denies them with the best of scientific consciences.

To avoid the problems with a ruling theory and the single working hypothesis (which can degenerate into a ruling theory), Chamberlin (1890) proposed the method of multiple working hypotheses, namely the development of various hypothesis that might explain the phenomenon under consideration. In support of the method of multiple working hypotheses, Chamberlin (1890) noted that:

> the re-action of one hypothesis upon another tends to amplify the recognized scope of each, and their mutual conflicts whet the discriminative edge of each.

9.2. Application to tumorigenesis

In the study of carcinogenesis, the ruling theory for at least sixty years has been the somatic mutation theory, consisting of successive driver mutations leading to clonal expansions (Baker 2012). Echoing the writings of Chamberlin and James on the problems with a ruling theory, Rous (1959) expressed concern about the ruling somatic mutation theory:

> numerous workers on cancer are now content to think it [cancer] results from somatic mutations. Hence they see no other reason to seek in other directions to learn its nature.

The somatic mutation theory is not as firmly established as might appear. There are many paradoxical results under the somatic mutation theory discussed here and elsewhere (Baker 2015). Bioinformatics methods can only prioritize driver mutations in humans (Cheng, Zhao, Zhao 2016), so cannot unambiguously prove their existence.

It is helpful to classify working hypotheses for tumorigenesis in terms of the role of cell-level change (such as genetic mutations, alterations of genetic pathways, epigenetic changes, or damage to mitochondria) and the role of tissue-level change (primarily disruption of tissue regulatory controls). Table 1 lists some working hypotheses for which a cell-level change is the primary driver of tumorigenesis. Table 1 includes the Somatic Mutation Theory (although that name is not used by its proponents) as well as variations of the Somatic Mutation Theory in which the microenvironment or cell-extrinsic factors play an important secondary role.

Somatic Mutation Theory: Cancer arises from a succession of driver mutations and clonal expansions.	Vogelstein et al 2013
Cancer arises from genetic and epigenetic changes channeled through the epigenome.	Feinberg 2018
Cancer immunoediting: Cancer arises from immunosurveillance selecting genetic variants.	Mittal et al 2014
Cancer is an atavistic condition involving genetic and epigenetic malfunctions.	Davies and Lineweaver, 2011

Cancer arises from cancer stem cells which arise from genetic mutations or cell transformation.	Yu et al 2012
Cancer arises from damage to the mitochondria.	Seyfried 2015
Cancer arises from oncogenic signaling pathways in which intrinsically disordered proteins exert a primary role.	Russo et al, 2016
Cancer arises from the selection of genetic and epigenetic variants in the context of the microenvironment.	Pepper et al 2014
Cancer arises from genome-mediated cellular evolution involving system stress and population diversity.	Horne, Pollick, and Heng, 2015
Cancer arises from genetic changes modified by the extracellular matrix.	Pickup, Mouw, and Weaver 2014
Cancer arises from genetic and epigenetic modifications facilitated by chronic fibrosis.	Rybinski, Franco-Barraza, and Cukierman 2014
Cancers are attractor states in gene networks modulated by cell-extrinsic factors.	Huang 2011

Table 1. Some working hypotheses for which a cell-level change is the primary driver of tumorigenesis.

Table 2 lists some working hypotheses for which tissue-level change is the primary driver of tumorigenesis. Table 2 includes the landmark Tissue Organization Field Theory (Sonnenschein and Soto 2016). Table 2 also includes working hypotheses (including the detached perictye hypothesis) in which mutations, under some circumstances, can play a secondary role in leading to the disruption of tissue regulatory controls.

Tissue organization field theory: Cancer arises from a breakdown of tissue organization involving many cells from different embryological layers, where proliferation is the default state of all cells.	Sonnenschein et al 2014; Sonnenschein and Soto 2016
Cancer arises from morphogenetic factors and thermodynamic constraints.	Bizzari et al 2011
Cancer arises from miscommunication in the region of developing disease.	Tarin 2011
Cancer is a disorder of patterning information in which cells stop maintaining higher order structure.	Moore, Walker, and Levin, 2017
Cancer arises from a sequence of pathological stimulus, chronic inflammation, fibrosis, a pre-cancerous niche, chronic stress escape, and transition of normal cell to a cancer cell.	Brücher and Jamall 2014
Cancer arise from progressive deregulation of tissue architecture, which leads to physical changes in cells and altered mechanical signaling.	Ingber 2008
Cancer arises from a disruption of morphostats which can sometimes arise from genetic changes.	Baker 2015
Detached pericyte hypothesis: Cancer arises from detached pericytes that induce fibrosis and form mesenchymal stem cells that adhere to fibrotic tissue.	This article

Table 2. Some working hypotheses for which a tissue-level change is the primary driver of tumorigenesis.

Table 3 lists working hypothesis in which both cell-level and tissue-level changes play major roles in tumorigenesis.

Cancer arises from altered tissue pattern formation, which, in turn, arises from altered molecular pathways.	Marongiu et al 2012
Cancer arises from a disruption of the tissue equilibrium as the initiator event and genetic alterations as tumor "promoters."	Capp 2017
Cancer arises from genetic changes that lead to a disruption of the morphostatic fields that maintain normal tissue microarchitecture.	Potter 2007
Cancer is a robust state in a network involving cell and tissue modules.	Yuan et al 2017

Table 3. Some working hypotheses for which a combination of cell-level changes and tissue-level changes drive tumorigenesis..

Creating a new hypothesis by combining multiple hypothesis, each explaining a subset of phenomena, is not recommended because it would have limited predictive value for new phenomena -- analogous to overfitting in machine learning, where a complex

model fits idiosyncrasies in one data set to such a degree that it poorly predicts outcomes in a new data set (Hand, 2006).

Ideally, one would try to see how well different working hypothesis explain each puzzling phenomenon in tumorigenesis. For example, consider the experimental result from foreign-body tumorigenesis that filter implants with small, but not large, pore sizes induce fibroid capsules and tumors (Karp et al 1973). The somatic mutation theory might suggest that small pore sizes block agents responsible for mutations. The immunosurveillance hypothesis might suggest that small pore sizes block infiltration into the fibroid capsules of cells that inhibit tumorigenesis. The hypothesis of disruption of morphostats suggests that only small pore sizes block the morphostats (Baker et al 2009). The detached pericyte hypothesis suggests that only small pores induce fibrosis, which is a prerequisite for tumorigenesis. Other hypotheses might involve other cells in the foreign-body reaction including monocytes, macrophages, and fibroblasts.

10. Conclusion

The detached pericyte hypothesis offers novel explanations for many puzzling phenomena in tumorigenesis. To avoid "cherry-picking", an attempt was made to include important puzzling phenomena even if the explanation under the detached pericyte hypothesis was speculative. It is important to try to explain puzzling phenomena rather than ignore them. As James (1890) wrote. "Anyone will renovate his science who will steadily look after the irregular phenomena." Similarly, the physicist Niels Bohr said "How wonderful that we have met with a paradox. Now we have some hope of making progress" (Moore 1966). The investigation of puzzling phenomena in tumorigenesis guided by the detached pericyte hypothesis and other working hypotheses should improve the understanding of tumorigenesis and provide new directions for cancer prevention research.

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