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# Introducing the Prodotis M1-Macrophage Hypothesis of Cancer Metastasis (PMMH)

**Soroush Niknamian* and Somayeh Zaminpira**

*Ph.D. in Cellular and Molecular Biology, University of Cambridge, United Kingdom*

***Corresponding Author:** Dr. Soroush Niknamian, Ph.D. in Cellular and Molecular Biology, University of Cambridge, United Kingdom.

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## Abstract

Our aim in this meta-analysis review is to find the real reason of the metastasis and to predict the next body tissue where the cancer tumor would metastasize. To find the best answer, we have reviewed the cases from 1889 to 2017 in humans, animals and plants tumors. Metastasis involves a complex series of steps in which cancer cells leave the original tumor site and migrate to other parts of the body. The macrophage type M1, seems the main cause of metastasis in humans and animal cancers. In plants, we have not found any case of metastasis and the reason is that they lack the macrophages. Nearly all metastasis hypothesis cannot bring out the next target tissue by even 80%, however; the most correct hypothesis is James Ewing's theory which challenged the seed and soil theory and proposed that metastasis occurs purely by anatomic and mechanical routes. By putting together all the findings and data from the mentioned dates, we have put forth a new hypothesis which could explain the main reason behind the metastasis of cancer tumors and predict the next tissue where the cancer will metastasize.

***Keywords:*** *Metastasis; Macrophage; James Ewing Theory; Plant Tumors; Animal Tumors; Human Tumors*

## Introduction

### Evolutionary Metabolic Hypothesis of Cancer (EMHC)

The first living cells on Earth are thought to have arisen more than 3.5 billion years ago, when the Earth was not more than about 109 years old. The environment lacked oxygen but was presumably rich in geochemically produced organic molecules, and some of the earliest metabolic pathways for producing ATP may have resembled present-day forms of fermentation. In the process of fermentation, ATP is made by a phosphorylation event that harnesses the energy released when a hydrogen-rich organic molecule, such as glucose, is partly oxidized. The electrons lost from the oxidized organic molecules are transferred via NADH or NADPH to a different organic molecule or to a different part of the same molecule, which thereby becomes more reduced. At the end of the fermentation process, one or more of the organic molecules produced are excreted into the medium as metabolic waste products. Others, such as pyruvate, are retained by the cell for biosynthesis [S. Zaminpira, S. Niknamian, ECRONICON, 2017]. The excreted end-products are different in different organisms, but they tend to be organic acids. Among the most important of such products in bacterial cells are lactic acid which also accumulates in anaerobic mammalian glycolysis, and formic, acetic, propionic, butyric, and succinic acids. The first cell on the earth before the entrance of the bacteria did contain nucleus and used the fermentation process to produce ATP for its energy. Then an aerobic proteo-bacterium enters the eukaryote either as a prey or a parasite and manages to avoid digestion. It then became an endosymbiont. As we observe, the fermentation process used the glucose or even glutamine to produce ATP, but the aerobic process used the glucose, fat and protein to produce more ATP than the previous one. The symbio-genesis of the mitochondria is based on the natural selection of Charles Darwin. Based on Otto Warburg Hypothesis, in nearly all cancer cells, the mitochondrion is shut down or are defected and the cancer cell do not use its

mitochondrion to produce ATP. This process of adaptation is based on Lamarckian Hypothesis of Evolution and the normal cells goes back to the most primitive time of evolution to protect itself from apoptosis and uses the fermentation process like the first living cells 1.5 billion years ago. Therefore, cancer is an evolutionary metabolic disease which uses glucose as the main food to produce ATP and Lactic Acid. The prime cause of cancer is the abundance of Reactive Oxygen Species produced by mitochondria that is a threat to the living normal cell and causes mitochondrial damage mainly in its cristae [S. Zaminpira, S. Niknamian, LAP Lambert Publishing, 2017].

## Metastasis

Metastasis is a pathogenic agent's spread from an initial or primary site to a different or secondary site within the host's body [1], yet is typically spoken of as such spread by a cancerous tumor [2]. The newly pathological sites, then, are metastases [3,4].

Cancer occurs after cells are genetically altered to proliferate rapidly and indefinitely. This uncontrolled proliferation by mitosis produces a primary heterogenetic tumour. The cells which constitute the tumor eventually undergo metaplasia, followed by anaplasia then dysplasia, resulting in a malignant phenotype. This malignancy allows for invasion into the circulation, followed by invasion to a second site for tumorigenesis [5].

Some cancer cells known as circulating tumor cells acquire the ability to penetrate the walls of lymphatic or blood vessels, after which they are able to circulate through the bloodstream to other sites and tissues in the body. This process is known (respectively) as lymphatic or hematogenous spread [6]. After the tumor cells come to rest at another site, they re-penetrate the vessel or walls and continue to multiply, eventually forming another clinically detectable tumor. This new tumor is known as a metastatic (or secondary) tumor. Metastasis is one of the hallmarks of cancer, distinguishing it from benign tumors [7]. Most cancers can metastasize, although in varying degrees. Basal cell carcinoma for example rarely metastasizes [8].

When tumor cells metastasize, the new tumor is called a secondary or metastatic tumor, and its cells are similar to those in the original or primary tumor [9]. This means that if breast cancer metastasizes to the lungs, the secondary tumor is made up of abnormal breast cells, not of abnormal lung cells. The tumor in the lung is then called metastatic breast cancer, not lung cancer. Metastasis is a key element in cancer staging systems such as the TNM staging system, where it represents the "M". In overall stage grouping, metastasis places a cancer in Stage IV. The possibilities of curative treatment are greatly reduced, or often entirely removed, when a cancer has metastasized [10].

## Metastasis and primary cancer

It is theorized that metastasis always coincides with a primary cancer, and, as such, is a tumor that started from a cancer cell or cells in another part of the body [11]. However, over 10% of patients presenting to oncology units will have metastases without a primary tumor found. In these cases, doctors refer to the primary tumor as "unknown" or "occult," and the patient is said to have cancer of unknown primary origin (CUP) or unknown primary tumors (UPT). It is estimated that 3% of all cancers are of unknown primary origin. Studies have shown that, if simple questioning does not reveal the cancer's source (coughing up blood-"probably lung", urinating blood-"probably bladder"), complex imaging will not either. In some of these cases a primary tumor may appear later [12].

## Macrophage

Macrophages are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, cancer cells, and anything else that does not have the types of proteins specific to healthy body cells on its surface [13] in a process called phagocytosis. These large phagocytes are found in essentially all tissues [14], where they patrol for potential pathogens by amoeboid movement. They take various forms (with various names) throughout the body (e.g., histiocytic, Kupffer cells, alveolar macrophages, microglia, and others), but all are part of the mononuclear phagocyte system. Besides phagocytosis, they play a critical role in nonspecific defense (innate immunity) and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. For example, they are important as antigen presenters to T cells. In humans, dysfunctional macrophages cause severe diseases such as chronic granulomatous disease that result in frequent infections [15].

Beyond increasing inflammation and stimulating the immune system, macrophages also play an important anti-inflammatory role and can decrease immune reactions through the release of cytokines [16]. Macrophages that encourage inflammation are called M1 macrophages, whereas those that decrease inflammation and encourage tissue repair are called M2 macrophages [17]. This difference is reflected in their metabolism; M1 macrophages have the unique ability to metabolize arginine to the "killer" molecule nitric oxide, whereas rodent M2 macrophages have the unique ability to metabolize arginine to the "repair" molecule ornithine [18].

Human macrophages are about 21 micrometres (0.00083 in) in diameter [19] and are produced by the differentiation of monocytes in tissues. They can be identified using flow cytometry or immunohistochemical staining by their specific expression of proteins such as CD14, CD40, CD11b, CD64, F4/80 (mice)/EMR1 (human), lysozyme M, MAC-1/MAC-3 and CD68 [20-22].

## Macrophage subtypes

Some believe that there are several activated forms of macrophages [23]. In spite of a spectrum of ways to activate macrophages, there are two main groups designated M1 and M2. M1 macrophages: as mentioned earlier (previously referred to as classically activated macrophages) [24], M1 "killer" macrophages are activated by LPS and IFN-gamma, and secrete high levels of IL-12 and low levels of IL-10. In contrast, the M2 "repair" designation (also referred to as alternatively activated macrophages) broadly refers to macrophages that function in constructive processes like wound healing and tissue repair, and those that turn off damaging immune system activation by producing anti-inflammatory cytokines like IL-10. M2 is the phenotype of resident tissue macrophages, and can be further elevated by IL-4. M2 macrophages produce high levels of IL-10, TGF-beta and low levels of IL-12. Tumor-associated macrophages are mainly of the M2 phenotype, and seem to actively promote tumor growth [25-27].

M1 macrophages promote atherosclerosis by inflammation. M2 macrophages can remove cholesterol from blood vessels, but when the cholesterol is oxidized, the M2 macrophages become apoptotic foam cells contributing to the atheromatous plaque of atherosclerosis [28-30].

## Materials and Methods

We have reviewed the cancer cases from 1889 to 2017 to find the best answer to the main reason of the metastasis in humans. For reaching the best answer to the body target which the tumor would metastasize, we have reviewed nearly the most important cases and studies in animals, humans and plant cancer tumors.

Metastasis involves a complex series of steps in which cancer cells leave the original tumor site and migrate to other parts of the body via the bloodstream, the lymphatic system, or by direct extension. To do so, malignant cells break away from the primary tumor and attach to and degrade proteins that make up the surrounding extracellular matrix (ECM), which separates the tumor from adjoining tissues [31]. By degrading these proteins, cancer cells are able to breach the ECM and escape. The location of the metastases is not always random, with different types of cancer tending to spread to particular organs and tissues at a rate that is higher than expected by statistical chance alone [32]. Breast cancer, for example, tends to metastasize to the bones and lungs. This specificity seems to be mediated by soluble signal molecules such as chemokines and transforming growth factor beta [33]. The body resists metastasis by a variety of mechanisms through the actions of a class of proteins known as metastasis suppressors, of which about a dozen are known [34].

Human cells exhibit three kinds of motion: collective motility, mesenchymal-type movement, and amoeboid movement. Cancer cells often opportunistically switch between different kinds of motion. Some cancer researchers hope to find treatments that can stop or at least slow down the spread of cancer by somehow blocking some necessary step in one or more kinds of motion [35].

Cancer researchers studying the conditions necessary for cancer metastasis have discovered that one of the critical events required is the growth of a new network of blood vessels, called tumor angiogenesis [36]. It has been found that angiogenesis inhibitors would therefore prevent the growth of metastases [37].

Initially, nearby lymph nodes are struck early [14]. The lungs, liver, brain, and bones are the most common metastasis locations from solid tumors [38].

Some patients, however, do not show any symptoms [39]. When the organ gets a metastatic disease it begins to shrink until its lymph nodes burst, or undergo lysis [40].

Metastatic tumors are very common in the late stages of cancer. The spread of metastasis may occur via the blood or the lymphatics or through both routes [41].

Several different cell types are critical to tumor growth. In particular, endothelial progenitor cells have been shown to have a strong influence on the growth of tumor blood-vessels. This finding was published in the journals *Science* (2008) and *Genes and Development* (2007) together with the fact that endothelial progenitor cells are critical for metastasis and angiogenesis [42]. A publication in *Cancer Research* (August 2010) confirmed the importance of endothelial progenitor cells in tumor growth, angiogenesis and metastasis. This seminal paper demonstrated that endothelial progenitor cells can be marked using the Inhibitor of DNA Binding 1 (ID1) [43]. This novel finding meant that investigators gained the ability to track endothelial progenitor cells from the bone marrow to the blood to the tumor-stroma and even incorporated in tumor vasculature. This finding of endothelial progenitor cells incorporated in tumor vasculature proves the importance of this cell type in blood-vessel development in a tumor setting and metastasis. Furthermore, ablation of the endothelial progenitor cells in the bone marrow can lead to a significant decrease in tumor growth and vasculature development. Therefore, endothelial progenitor cells are very important in tumor biology and present novel therapeutic targets [44].

NFAT transcription factors are implicated in breast cancer, more specifically in the process of cell motility at the basis of metastasis formation. Indeed, NFAT1 (NFATC2) and NFAT5 are pro-invasive and pro-migratory in breast carcinoma and NFAT3 (NFATc4) is an inhibitor of cell motility [45,46]. NFAT1 regulates the expression of the TWEAKR and its ligand TWEAK with the Lipocalin 2 to increase breast-cancer cell invasion and NFAT3 inhibits Lipocalin 2 expression to blunt the cell invasion [47].

Epigenetic regulation also plays an important role in the metastatic outgrowth of disseminated tumor cells. Metastases display alterations in histone modifications, such as H3K4-methylation and H3K9-methylation, when compared to matching primary tumors [48]. These epigenetic modifications in metastases may allow the proliferation and survival of disseminated tumor cells in distant organs [49].

Recently, a series of high-profile experiments suggests that the co-option of intercellular cross-talk mediated by exosome vesicles is a critical factor involved in all steps of the invasion-metastasis cascade [50].

### Metastasis occurs by the following four routes:

#### Transcoelomic

The spread of a malignancy into body cavities can occur via penetrating the surface of the peritoneal, pleural, pericardial, or subarachnoid spaces. For example, ovarian tumors can spread transperitoneally to the surface of the liver [51].

#### Lymphatic spread

Lymphatic spread allows the transport of tumor cells to regional lymph nodes near the primary tumor and ultimately, to other parts of the body. This is called nodal involvement, positive nodes, or regional disease. “Positive nodes” is a term that would be used by medical specialists to describe regional lymph nodes that tested positive for malignancy. It is common medical practice to test by biopsy at least one lymph node near a tumor site when carrying out surgery to examine or remove a tumor. This lymph node is then called a sentinel lymph node. Lymphatic spread is the most common route of initial metastasis for carcinomas [52]. In contrast, it is uncommon for a sarcoma to metastasize via this route. Localized spread to regional lymph nodes near the primary tumor is not normally counted as a metastasis, although this is a sign of a worse outcome. The lymphatic system does eventually drain from the thoracic duct and right lymphatic duct into the systemic venous system at the venous angle and into the brachiocephalic veins, and therefore these metastatic cells can also eventually spread through the haematogenous route [53,54].

### Hematogenous spread

This is typical route of metastasis for sarcomas, but it is also the favored route for certain types of carcinoma, such as renal cell carcinoma originating in the kidney. Because of their thinner walls, veins are more frequently invaded than are arteries, and metastasis tends to follow the pattern of venous flow. That is, hematogenous spread often follows distinct patterns depending on the location of the primary tumor. For example, colorectal cancer spreads primarily through the portal vein to the liver [55].

### Canalicular spread

Some tumors, especially carcinomas may metastasize along anatomical canalicular spaces. These spaces include for example the bile ducts, the urinary system, the airways and the subarachnoid space. The process is similar to that of transcoelomic spread. However, often it remains unclear whether simultaneously diagnosed tumors of a canalicular system are one metastatic process or in fact independent tumors caused by the same agent (field cancerization) [56].

### Organ-specific targets

There is a propensity for certain tumors to seed in particular organs. This was first discussed as the "seed and soil" theory by Stephen Paget over a century ago, in 1889. The propensity for a metastatic cell to spread to a particular organ is termed 'organotropism'. For example, prostate cancer usually metastasizes to the bones. In a similar manner, colon cancer has a tendency to metastasize to the liver. Stomach cancer often metastasises to the ovary in women, then it is called a Krukenberg tumor [57].

In 1829, Récamier recognized that cancer can spread from a primary tumor and coined the term "metastasis" from the Greek "methistemi", meaning to change or displace [58]. Paget's "seed and soil" theory explained the non-random pattern of cancer metastasis in 1889 when he postulated that factors within the metastatic site promoted growth in the same way that fertile soil allows the successful growth of seeds. In a complementary hypothesis, James Ewing proposed in 1928 that cancer cells were directed to that site by the direction of lymphatic and circulatory systems [59].

From the perspective of species migration, both Paget's and Ewing's theories are correct. Migration is subdivided into emigration (the act of leaving), migration (the act of travelling), and immigration (the process of arriving) [60]. In the paradigm of migration, Ewing focused on the migration step and Paget focused on immigration [61,62]. Ewing's theory accounts for the migration of prostate cancer cells to the lumbar vertebrae via Batson's plexus of draining lymph nodes and Paget's theory helps explain the organ specificity of prostate cancer metastases to bone. Fidler further refined the seed/soil hypothesis in 2003 to take into account the emigration step [63]. First, primary tumors contain heterogeneous subpopulations of cells with different angiogenic, invasive and metastatic properties (properties that promote emigration). The metastatic process is then selective for cells that can successfully survive migration to the distal target organ. The successful proliferation of metastatic cells depends on the ability of these cells to interact and utilize the soil of the new microenvironment [64]. According to the "seed and soil" theory, it is difficult for cancer cells to survive outside their region of origin, so in order to metastasize they must find a location with similar characteristics [65]. For example, breast tumor cells, which gather calcium ions from breast milk, metastasize to bone tissue, where they can gather calcium ions from bone. Malignant melanoma spreads to the brain, presumably because neural tissue and melanocytes arise from the same cell line in the embryo [66].

James Ewing challenged the seed and soil theory and proposed that metastasis occurs purely by anatomic and mechanical routes [67]. This hypothesis has been recently utilized to suggest several hypotheses about the life cycle of circulating tumor cells (CTCs) and to postulate that the patterns of spread could be better understood through a filter and flow perspective [68]. However, contemporary evidences indicate that the primary tumor may dictate organ tropic metastases by inducing the formation of pre-metastatic niches at distant sites, where incoming metastatic cells may engraft and colonize [69]. Specifically, exosome vesicles secreted by tumors have been shown to home to pre-metastatic sites, where they activate pro-metastatic processes such as angiogenesis and modify the immune contexture, so as to foster a favorable microenvironment for secondary tumor growth [70].

## Macrophages and Cancer

Macrophages are among the most versatile cells of the body with respect to their ability to migrate, to change shape, and to secrete growth factors and cytokines [71-73]. These macrophage behaviors are also the recognized behaviors of metastatic cells. Macrophages manifest two distinct polarization phenotypes: the classically activated (M1 phenotype) and the alternatively activated (M2 phenotype). Macrophages acquire the M1 phenotype in response to pro-inflammatory molecules and release inflammatory cytokines, reactive oxygen species, and nitric oxide [74-77]. In contrast, macrophages acquire the M2 phenotype in response to anti-inflammatory molecules such as IL-4, IL 13, IL-10 and to apoptotic cells [78]. M2 macrophages promote tissue remodeling and repair, but are immunosuppressive and poor antigen presenters [79]. Although the M1 and the M2 macrophages play distinct roles during tumor initiation and malignant progression, macrophage-epithelial cell fusions can involve either activation state [80].

M1 macrophages facilitate the early stages of tumorigenesis through the creation of an inflammatory microenvironment that can produce nuclear and mitochondrial damage [81,82]. However, TAM can also undergo a phenotypic switch to the M2 phenotype during tumor progression [83,84]. The TAM population comprising M2 macrophages scavenge cellular debris, promote tumor growth, and enhance angiogenesis. M2 macrophages also fuse with tumor cells, thus, expressing characteristics of both cell types. It has always been difficult to know for certain, however, whether TAM are part of the normal stroma or are part of the malignant cell population [85-87]. This is especially the case in human cancers [88,89].

Increasing evidence suggests that many of the myeloid/macrophage cells seen within human tumors are also part of the malignant cell population. Aichel first proposed over a century ago that tumor progression involved fusion between leukocytes and somatic cells [90-93]. Several human metastatic cancers express multiple molecular and behavioral characteristics of macrophages including phagocytosis, cell-cell fusion, and antigen expression. Tarin also considers the expression of osteopontin and CD44 as important for the regulatory gene group/network associated with metastasis [94]. This is interesting as there is strong evidence that both osteopontin and CD44 are expressed in monocytes and macrophages under various physiological and pathological states [95-98]. We argued that an origin of metastatic cancer from myeloid cells could account for many mesenchymal properties of metastatic cancers [99,100]. It is not, therefore, necessary to invoke an EMT to account for metastasis [101,102].

Interestingly, macrophages express most hallmarks of metastatic tumor cells when responding to tissue injury or disease. For example, monocytes (derived from hematopoietic bone marrow cells) extravasate from the vasculature and are recruited to the wound via cytokines released from the damaged tissue [103,104]. Within the wound, monocytes differentiate into alternatively-activated macrophages and dendritic cells where they release a variety of pro-angiogenic molecules including vascular endothelial growth factor, fibroblast growth factor, and platelet derived growth factor [105,106]. M2 macrophages also actively phagocytize dead cells and cellular debris [107]. On occasion, macrophages undergo homotypic fusion resulting in multinucleated giant cells with increased phagocytic capacity [108]. Following these wound-healing activities, macrophages intravasate back into the circulation where they travel to the lymph nodes to participate in the immune response [109].

Some phagocytic macrophages also migrate to lymph nodes and differentiate into dendritic cells [110]. These findings indicate that normal macrophages are capable of expressing all hallmarks of metastatic cancer cells including tissue invasion, release of pro-angiogenic molecules/cytokines, survival in hypoxic and necrotic environments, intravasation into the circulatory/lymphatic systems, and extravasation from these systems at distant locations. An EMT is not necessary to explain these behaviors, as they are already the evolutionary programmed behaviors of macrophages [111].

Macrophages contribute to tumor growth and progression. Attracted to oxygen-starved (hypoxic) and necrotic tumor cells they promote chronic inflammation. Inflammatory compounds such as tumor necrosis factor (TNF)-alpha released by the macrophages activate the gene switch nuclear factor-kappa B. NF-κB then enters the nucleus of a tumor cell and turns on production of proteins that stop apop-

tosis and promote cell proliferation and inflammation [112]. Moreover, macrophages serve as a source for many pro-angiogenic factors including vascular endothelial factor (VEGF), tumor necrosis factor-alpha (TNF-alpha), macrophage colony-stimulating factor (M-CSF/CSF1) and IL-1 and IL-6 contributing further to the tumor growth. Macrophages have been shown to infiltrate a number of tumors. Their number correlates with poor prognosis in certain cancers including cancers of breast, cervix, bladder and brain [113-116]. Tumor-associated macrophages (TAMs) are thought to acquire an M2 phenotype, contributing to tumor growth and progression. Research in various study models suggests that the co-operation of T-cells and macrophages is important to suppress tumors. This co-operation involves not only the direct contact of T-cell and macrophage, with antigen presentation, but also includes the secretion of adequate combinations of cytokines, which enhance T-cell antitumor activity [117,118]. Recent study findings suggest that by forcing IFN-α expression in tumor-infiltrating macrophages, it is possible to blunt their innate protumoral activity and reprogram the tumor microenvironment toward more effective dendritic cell activation and immune effector cell cytotoxicity [119,120].

## Macrophage Facilitation of Metastasis

It has long been recognized that many malignant tumors contain significant numbers of macrophages and other cells of the stroma [121]. The macrophages present in tumors are generally referred to as tumor-associated macrophages (TAM). TAM can establish the premetastatic niche, while enhancing tumor inflammation and angiogenesis [122]. In other words, TAM facilitate the metastatic cascade. While gene mutations are still thought to initiate neoplasia under this model, it is the stromal macrophages acting as cellular chaperones that facilitate tumor development, progression, and the eventual seeding of metastasis [123]. The stromal TAM are viewed as essential participants in all phases of metastasis, but are not considered neoplastic themselves [124]. However, we recently reviewed evidence showing that many human metastatic tumors also contain neoplastic cells with macrophage properties [125]. It is not easy to distinguish neoplastic from non-neoplastic macrophages in the inflamed tumor microenvironment, as both cells are similar in gene expression, morphology, and function [126,127]. In contrast to the view that macrophages serve as accessories or cellular chaperones for the metastatic cascade of neoplastic stem cells, we consider the metastatic cells themselves as derived from macrophages or other similar cells of myeloid origin [128,129].

## Linking metastasis to mitochondrial dysfunction

Substantial evidence now indicates that nearly all cancers are a type of mitochondrial disease arising from respiratory insufficiency [130]. This damage leads to fermentation as a compensatory source of energy according to the original theory of Warburg [131]. When permanent respiratory damage occurs in cells of myeloid origin including hematopoietic stem cells and their fusion hybrids, metastasis would be a potential outcome. It is not necessary to blame mutations or to invent complicated genetic regulatory systems to explain the phenomenon of metastasis [132,133].

Numerous studies indicate that mitochondria from a broad range of metastatic cancers are abnormal and incapable of generating energy through normal respiration [134,135]. Energy through fermentation is the single most common hallmark of all cancer cells including those with metastatic potential. This phenotype arises from mitochondrial dysfunction [136]. Mitochondrial damage can arise in any cell within the inflammatory microenvironment of the incipient tumor including TAM, homotypic fusion hybrids of hematopoietic cells, or heterotypic fusion hybrids of macrophages and neoplastic epithelial cells [137]. The end result would be cells with metastatic potential. Although metastatic cells will differ in their morphology from one organ system to the next, they all suffer from the common malady of insufficient respiration. The origin of metastatic cancer from myeloid cells and fusion hybrids can explain the substantial morphological and genetic diversity seen among different tumor types [138]. Metastasis can arise in macrophage fusion hybrids that sustain irreversible mitochondrial damage [139].

## Respiratory Damage in Macrophage Fusion Hybrids

Substantial evidence indicates that normal mitochondrial function suppresses tumorigenesis [140]. Cytoplasm containing mitochondria with normal respiratory function can suppress tumorigenicity despite the continued presence of the tumor cell nucleus [141]. These findings indicate that nuclear gene mutations alone cannot account for the origin or progression of cancer. How do these findings relate

to the origin of metastatic cancer cells following macrophage fusions with other cells? If normal macrophages fuse with neoplastic stem cells, it might be anticipated that normal respiratory function of the macrophages would suppress tumorigenicity in the fused hybrid [142]. Although normal respiration would initially suppress tumorigenicity in fused hybrids, persistent or recurrent inflammation in the microenvironment will eventually damage the majority of mitochondria in the fused hybrids, thus initiating the path to metastasis [143]. As macrophages evolved to survive in hypoxic and inflammatory environments, considerable time and iterative damage to respiration would be necessary to initiate tumorigenesis in the fusion hybrids. It is also noteworthy that radiation exposure would not only enhance fusion hybrid formation, but would also damage respiration thus leading to compensatory fermentation and the onset of tumorigenesis. It should not be surprising why long-term survival is reduced or why more aggressive tumors recur in many patients that receive radiation to treat their cancers [144-146].

As respiration is responsible for maintaining genomic stability and the differentiated state, respiratory insufficiency will eventually induce the default state of unbridled proliferation and genomic instability [147]. If this occurs in cells of myeloid origin like macrophages, then emergence of cells with enhanced metastatic potential would be a predicted outcome. Macrophages are genetically programmed to exist in the circulation and to enter and exit tissues [148]. The dysregulated behavior of these cells through corrupted energy metabolism would have dire consequences. Oncogene activation and tumor suppressor-gene inactivation are required to maintain energy production through fermentation following irreversible injury to oxidative phosphorylation [149]. Enhanced glucose uptake seen in metastatic lesions under PET scanning is indicative of enhanced glycolysis and abnormal energy metabolism [150].

## Genetic heterogeneity in cancer metastasis

Considerable genetic heterogeneity is observed in comparing tumor tissue from primary growth sites with tissue from distant metastases [151-153]. Genetic heterogeneity is seen not only between patients with similar tumor histopathology, but also for the tumors growing at different sites within the same patient [154]. Almost every type of genetic heterogeneity imaginable from point mutations to major genomic rearrangements can be found in metastatic and highly invasive cancers including those from breast, brain, and pancreas [155]. The mostly non-uniform distribution of mutations in these tumors is consistent with findings that each neoplastic cell within a given tumor can have a profile of changes uniquely different from any other cell within the tumor [156-159]. Moreover, if the spread of metastatic cells to some organs (like liver and lung) occurs earlier than spread to other organs, it is possible that genetic heterogeneity would be greater in these organs than in organs that receive metastatic cells later in the disease progression. This is expected if the number of divisions is greater for tumor cells that arrive earlier in these organs than for tumor cells that arrive later in other organs. This could explain why genomic heterogeneity is more diverse in some organs than in other organs or in the primary tumor. These complications can obscure attempts to accurately define the clonal origin of tumor cells [160].

In their analysis of the genomic heterogeneity observed in pancreatic cancer, Campbell and colleagues conclude that, "the biological pathways underlying these forms of genomic instability remain unclear" [161]. As genomic stability is dependent on normal mitochondrial function, it should not be surprising that there is a "richness of genetic variation in cancer" as Campbell and co-workers describe [162]. The richness is the likely consequence of damaged respiration with compensatory fermentation in populations of fusion hybrids that differ from each other in genetic architecture. A non-uniform or random distribution of mutations can arise from the migration of these hybrid cells to other organs. The gene mutations also arise as downstream epiphenomena of respiratory insufficiency coupled with compensatory fermentation. As the linkage of genomic instability to mitochondrial dysfunction was not discussed in any of the cancer genome studies mentioned above, we can only assume that the investigators were unaware of this linkage. It is unfortunate that so many industrious investigators focus so much attention on the genomic instability of tumors, which is largely irrelevant to the disease. Real progress in cancer management will be realized only after the cancer field breaks its addiction to the gene theory and recognizes the centrality of mitochondrial damage in the origin and progression of the disease [163-165].

### Cancer in animals

Cancer incidence in the wolf is lower than that in the domestic dog. Cancer is low in the chimpanzee than in the human despite the two species having very similar cancer genes. The issue is not genetics, but it is the environment or gene-environmental interactions. Most chimpanzees eat their natural diet while in the wild or in captivity. It is likely that the incidence of cancer would be higher in chimpanzees that would eat a Western human diet. Germ line mutations might increase the incidence of some cancers, but only in a certain provocative environment. Cancer can occur in wild animals that are infected with certain viruses. Viruses can damage mitochondrial function thus producing cancer in the infected cells. The somatic mutations would arise as a downstream effect of the defective respiration. It is not clear if viral infections would be more common in domestic animals than in wild animals. Pollutants in the environment, including in the diet, would damage cellular respiration. Respiratory damage is largely responsible for cancer in both humans and domesticated animals that do not eat their natural foods. Cancer metastasis in animals is the same as humans [ S. Zaminpira, S. Niknamian, JMEST, 2017].

### Cancer in Plants (Gall)

Galls or cecidia are a kind of swelling growth on the external tissues of plants or animals. Plant galls are abnormal outgrowths of plant tissues, similar to benign tumors or warts in animals. They can be caused by various parasites, from fungi and bacteria, to insects and mites. Plant galls are often highly organized structures and because of this the cause of the gall can often be determined without the actual agent being identified. This applies particularly to some insect and mite plant galls [166].

### Cancer metastasis in plants

Although the Gall tumors in plants have been discussed thoroughly in this review, there has not been shown that cancer in plants could metastasize. The lack of macrophages in plants is the main answer that cancer in plants never metastasize which is the prime reason behind the differences between the animal and the plant cancers. All cancers in plants are benign and are not malignant tumors [218].

## Conclusion

Our meta-analysis review between 1889 to 2017 shows that the prime cause of metastasis in humans and animals are macrophages type M1 which by entering the cancerous cells would be cancerous and transport the cancer to the next tissue. There have been many cases of plant cancer tumors which is called Gall tumors. These tumors are caused by the outside parasites such as bacteria and viruses. Metastasis in plant tumors cannot occur since plants do not use and contain macrophages. Nearly all hypothesis behind the prediction of the target metastatic tissue cannot be correct except James Ewing hypothesis which have been introduces in 1928, challenged the seed and soil theory and proposed that metastasis occurs purely by anatomic and mechanical routes. James Ewing proposed in 1928 that cancer cells were directed to that site by the direction of lymphatic and circulatory systems. This hypothesis has been recently utilized to suggest several hypotheses about the life cycle of circulating tumor cells (CTCs) and to postulate that the patterns of spread could be better understood through a filter and flow perspective. In our perspective, the next tissue where the cancer would be metastasizing can be predicted by the amounts of inflammation in that tissue. The more inflammation, the more possibility of that tissue to be the target. Therefore; we introduce a new hypothesis which is more complete in the cause of cancer metastasis which we call it "Prodotis M1-Macrophage Hypothesis of Cancer Metastasis (PMMH)". This is the combination of the James Ewing Theory and Macrophage theory of metastasis and states that: "as respiration is responsible for maintaining genomic stability and the differentiated state, respiratory insufficiency will eventually induce the default state of unbridled proliferation and genomic instability. If this occurs in cells of myeloid origin like macrophages, then emergence of cells with enhanced metastatic potential would be a predicted outcome. Therefore; cancer metastasis is metabolically originated and the real cause of cancer metastasis is M1 macrophages by the means of lymphatic and circulatory systems, and the target tissue is where the most inflammation has been occurred".

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## Appendix

### Crown Gall Disease

*Agrobacterium tumefaciens* is the causal agent of crown gall disease (the formation of tumors) in over 140 species of eudicots. It is a rod-shaped, Gram-negative soil bacterium [167]. Symptoms are caused by the insertion of a small segment of DNA (known as the T-DNA, for 'transfer DNA', not to be confused with tRNA that transfers amino acids during protein synthesis, confusingly also called transfer RNA), from a plasmid, into the plant cell, which is incorporated at a semi-random location into the plant genome [168,169].

A. tumefaciens is an alpha-proteo-bacterium of the family Rhizobiaceae, which includes the nitrogen-fixing legume symbionts. Unlike the nitrogen-fixing symbionts, tumor-producing *Agrobacterium* species are pathogenic and do not benefit the plant. The wide variety of plants affected by *Agrobacterium* makes it of great concern to the agriculture industry [170].

Economically, *A. tumefaciens* is a serious pathogen of walnuts, grape vines, stone fruits, nut trees, sugar beets, horse radish, and rhubarb [171].

To be virulent, the bacterium must contain a tumour-inducing plasmid (Ti plasmid or pTi), of 200 kb, which contains the T-DNA and all the genes necessary to transfer it to the plant cell. Many strains of *A. tumefaciens* do not contain a pTi [172].

Since the Ti plasmid is essential to cause disease, prepenetration events in the rhizosphere occur to promote bacterial conjugation - exchange of plasmids amongst bacteria. In the presence of opines, *A. tumefaciens* produces a diffusible conjugation signal called 30C8HSL or the *Agrobacterium* autoinducer. This activates the transcription factor TraR, positively regulating the transcription of genes required for conjugation [173].

*A. tumefaciens* infects the plant through its Ti plasmid. The Ti plasmid integrates a segment of its DNA, known as T-DNA, into the chromosomal DNA of its host plant cells. *A. tumefaciens* has flagella that allow it to swim through the soil towards photoassimilates that accumulate in the rhizosphere around roots. Some strains may chemotactically move towards chemical exudates from plants, such as acetosyringone and sugars. The former is recognised by the VirA protein, a transmembrane protein encoded in the virA gene on the Ti plasmid. Sugars are recognised by the chvE protein, a chromosomal gene-encoded protein located in the periplasmic space [174].

At least 25 vir genes on the Ti plasmid are necessary for tumor induction. In addition to their perception role, virA and chvE induce other vir genes. The virA protein has autokinase activity: it phosphorylates itself on a histidine residue. Then the virA protein phosphorylates the virG protein on its aspartate residue. The virG protein is a cytoplasmic protein produced from the virG Ti plasmid gene. It is a transcription factor, inducing the transcription of the vir operons. The chvE protein regulates the second mechanism of the vir genes' activation. It increases VirA protein sensitivity to phenolic compounds [175-177].

Attachment is a two-step process. Following an initial weak and reversible attachment, the bacteria synthesize cellulose fibrils that anchor them to the wounded plant cell to which they were attracted. Four main genes are involved in this process: *chvA, chvB, pscA*, and *att*. The products of the first three genes apparently are involved in the actual synthesis of the cellulose fibrils. These fibrils also anchor the bacteria to each other, helping to form a microcolony [178,179].

VirC, the most important virulent gene, is a necessary step in the recombination of illegitimate recolonization. It selects the section of the DNA in the host plant that will be replaced and it cuts into this strand of DNA [180].

After production of cellulose fibrils, a calcium-dependent outer membrane protein called rhicadhesin is produced, which also aids in sticking the bacteria to the cell wall. Homologues of this protein can be found in other rhizobia [181].

### Possible plant compounds that initiate *Agrobacterium* to infect plant cells [182]:

To transfer the T-DNA into the plant cell, *A. tumefaciens* uses a type IV secretion mechanism, involving the production of a T-pilus. When acetosyringone and other substances are detected, a signal transduction event activates the expression of 11 genes within the VirB operon which are responsible for the formation of the T-pilus [183].

The pro-pilin is formed first. This is a polypeptide of 121 amino acids which requires processing by the removal of 47 residues to form a T-pilus subunit. The subunit is circularized by the formation of a peptide bond between the two ends of the polypeptide [184].

Products of the other VirB genes are used to transfer the subunits across the plasma membrane. Yeast two-hybrid studies provide evidence that VirB6, VirB7, VirB8, VirB9 and VirB10 may all encode components of the transporter. An ATPase for the active transport of the subunits would also be required [185].

The T-DNA must be cut out of the circular plasmid. A VirD1/D2 complex nicks the DNA at the left and right border sequences. The VirD2 protein is covalently attached to the 5' end. VirD2 contains a motif that leads to the nucleoprotein complex being targeted to the type IV secretion system (T4SS) [186].

In the cytoplasm of the recipient cell, the T-DNA complex becomes coated with VirE2 proteins, which are exported through the T4SS independently from the T-DNA complex. Nuclear localization signals, or NLSs, located on the VirE2 and VirD2, are recognised by the importin alpha protein, which then associates with importin beta and the nuclear pore complex to transfer the T-DNA into the nucleus. VIP1 also appears to be an important protein in the process, possibly acting as an adapter to bring the VirE2 to the importin. Once inside the nucleus, VIP2 may target the T-DNA to areas of chromatin that are being actively transcribed, so that the T-DNA can integrate into the host genome [187-190].

### Genes in the T-DNA

### Hormones

To cause gall formation, the T-DNA encodes genes for the production of auxin or indole-3-acetic acid via the IAM pathway. This biosynthetic pathway is not used in many plants for the production of auxin, so it means the plant has no molecular means of regulating it and auxin will be produced constitutively. Genes for the production of cytokinins are also expressed. This stimulates cell proliferation and gall formation [191].

### Opines

The T-DNA contains genes for encoding enzymes that cause the plant to create specialized amino acid derivatives which the bacteria can metabolize, called opines [192]. Opines are a class of chemicals that serve as a source of nitrogen for *A. tumefaciens*, but not for most other organisms. The specific type of opine produced by *A. tumefaciens* C58 infected plants is nopaline (Escobar et al., 2003).

Two nopaline type Ti plasmids, pTi-SAKURA and pTiC58, were fully sequenced. *A. tumefacien*s C58, the first fully sequenced pathovar, was first isolated from a cherry tree crown gall. The genome was simultaneously sequenced by Goodner., et al. and Wood., *et al*. in 2001. The genome of *A. tumefaciens* C58 consists of a circular chromosome, two plasmids, and a linear chromosome. The presence of a covalently bonded circular chromosome is common to Bacteria, with few exceptions. However, the presence of both a single circular chromosome and single linear chromosome is unique to a group in this genus. The two plasmids are pTiC58, responsible for the processes involved in virulence, and pAtC58, dubbed the "cryptic" plasmid [193,194].

The pAtC58 plasmid has been shown to be involved in the metabolism of opines and to conjugate with other bacteria in the absence of the pTiC58 plasmid. [195] If the pTi plasmid is removed, the tumor growth that is the means of classifying this species of bacteria does not occur [196].

## Different kinds of Galls

1. Ash flower gall: this gall is caused by a small mite that causes irregular distortion of male flowers. The galls are initially green, then dry and turn brown [197].

2. Ash midrib gall: normally 0.5 to 1 inch long, these galls are succulent and have thick walls. A small cavity within each gall contains one or more small maggots, the larval stages of very small flies called midges. Female midges lay their eggs in very young leaflets during early spring. Gall formation begins soon after the eggs are laid. Specifics of the biology of this insect are not known. The galls probably do not harm tree health [198].

3. Elm cockscomb gall: these distinct galls, caused by an aphid, are about one inch long and about 1/4 inch high. The irregular edge of the gall and its red color at maturity account for the common name. The galls dry, harden and turn brown as they age. Aphids may be seen through a slit-like opening in the underside of the gall. This insect has a complex life cycle-it forms galls on elm in early summer, then feeds on grass roots later in the summer. The galls apparently do not cause significant harm to the tree [199].

4. Hackberry leaf gall: this gall is caused by a small (0.1 inch long) aphid-like insect with sucking mouthparts called a jumping plant louse. The adults spend the winter under bark crevices and can invade houses in large numbers in the fall. Females lay eggs over a long period of time beginning when leaves begin to unfold from the buds in the spring. Feeding by the nymphs that hatch from these eggs causes abnormal plant growth that forms a pouch. The psyllids remain inside the galls until they emerge as adults in late summer to early fall. There is one generation each year. Heavy infestations can result in premature leaf drop which over a series of years may affect tree health [200].

5. Honeylocust pod gall: this gall is caused by a small fly (midge). The sunburst cultivar appears to be very susceptible to this pest. Infested leaves have globular or pod-like distortions that contain one to several small maggots (0.25 inch long). Infestations begin when females lay eggs in young leaflets. There are five or more generations each year. Infested leaves often drop prematurely and repeated damage can kill small branches. New shoots develop at the base of dead twigs. As a result, the natural shape of the tree may be lost [201,202].

6. Oak gall

7. Petiole and stipule galls: thick globe-like galls can develop on leaf petioles and stems. Many of these are caused by insects called phylloxerans which are very similar to aphids. The hard, woody galls may remain on the tree for several years. Usually, there is one generation each year and the insects over winter on the tree in the egg stage [203].

8. Willow shoot galls: these swellings on shoots, twigs, or leaf petioles, may be caused by small flies (midges) or small wasps (saw-flies). The gall increases in size as long as the immature stages are active. They cause no significant injury. The infestation may be reduced by pruning and destroying the galled areas before the adult insect emerges, usually in late summer [204].

9. Witchhazel gall: this gall is caused by an aphid that passes the winter in eggs laid on twigs of the plant. Feeding by the aphid causes the formation of conical galls on the upper side of the leaf. Each gall, produced by a single aphid, later becomes filled with off-spring. Mature aphids with wings leave the galls in late spring and early summer and fly to birch. After several generations there, the insects return to witch hazel to lay the eggs that survive the winter. No galls are formed on the birch [205].

Many rust fungi induce gall formation, including western gall rust, which infects a variety of pine trees and cedar-apple rust. Galls are often seen in *Millettia pinnata* leaves and fruits. Leaf galls appear like tiny clubs; however, flower galls are globose. *Exobasidium* often induces spectacular galls on its hosts [206].

The fungus *Ustilago esculenta* associated with *Zizania latifolia*, a wild rice, produces an edible gall highly valued as a food source in the Zhejiang and Jiangsu provinces of China [207].

### Bacteria and viruses

*Agrobacterium tumefaciens* and *Pseudomonas savastanoi* are examples of gall-causing bacteria. Gall forming virus was found on rice plants in central Thailand in 1979 and named rice gall dwarf. Symptoms consisted of gall formation along leaf blades and sheaths, dark green discoloration, twisted leaf tips and reduced numbers of tillers. Some plants died in the glasshouse in later stages of infection. The causal agent was transmitted by *Nephotettix nigropictus* after an incubation of two weeks. Polyhedral particles of 65 nm diameter in the cytoplasm of phloem cells were always associated with the disease. No serologic relationship was found between this virus and that of rice dwarf [208-210].

### Nematodes

Nematodes are microscopic worms that live in the soil. Some nematodes (*Meloidogyne* species or root-knot nematodes) cause galls on the roots of susceptible plants [211]. The galls are small, individual and beadlike in some hosts. In other plant species galls may be massive accumulations of fleshy tissue more than an inch in diameter. Some ectoparasitic nematodes (nematodes that live outside the plant in the soil), such as sting and stubby-root nematodes, may cause root tips to swell. Nitrogen-fixing bacteria (*Rhizobium* species) cause swellings on the roots of most legumes (such as clover, peas and beans) [212]. These swellings, called nodules, are easily distinguished from root-knot galls by differences in how they are attached to the root and their contents. Nodules are loosely attached to the root, while root-knot galls originate from infection at the center of the root, so they are an integral part of the root. In addition, fresh *Rhizobium* nodules have a milky pink-to-brown liquid inside them, while root-knot galls have firmer tissues and contain female root-knot nematodes (creamy white beads less than 1/32 inch in diameter) inside the gall tissues [213].

### Insect Galls

Insect galls are the highly distinctive plant structures formed by some herbivorous insects as their own microhabitats. They are plant tissue which is controlled by the insect. Galls act as both the habitat and food source for the maker of the gall. The interior of a gall can contain edible nutritious starch and other tissues. Some galls act as "physiologic sinks", concentrating resources in the gall from the surrounding plant parts [214]. Galls may also provide the insect with physical protection from predators [215].

Insect galls are usually induced by chemicals injected by the larvae or the adults of the insects into the plants, and possibly mechanical damage. After the galls are formed, the larvae develop inside until fully grown, when they leave. In order to form galls, the insects must take advantage of the time when plant cell division occurs quickly: the growing season, usually spring in temperate climates, but which is extended in the tropics [216].

The meristems, where plant cell division occurs, are the usual sites of galls, though insect galls can be found on other parts of the plant, such as the leaves, stalks, branches, buds, roots, and even flowers and fruits. Gall-inducing insects are usually species-specific and sometimes tissue-specific on the plants they gall [217].

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