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The molecular connections between lung and pancreatic cancer metastases: are we not seeing the forest for the trees?

Abstract

Metastases to the pancreas are rare at 1-2%. Among primaries metastasizing to the pancreas, lung cancer (LC) is frequently the culprit. Metastases to the lung from pancreatic cancer (PC) are significantly more common at about 45%, presenting striking differences in cancer behavior. There are conflicting reports regarding cancerogenicity and metastatic incidence between the lung and pancreas. Therefore, this review takes a fresh look at lung and pancreatic cancer behavior. Secondary metastases to the lung and pancreas are often indistinguishable from LC and PC primaries, and the seed and soil hypothesis is not always congruous with clinical interpretation of disease course. Sometimes single "seed" dissemination is thought to occur at the preneoplastic stage without any evidence of tumor invasion. Metastatic growth may become dormant, manifesting years later as cancer of unknown primary (CUP). Interestingly, CUPs are discovered to originate most frequently from LC and PC primaries at autopsy. The lung and pancreas are morphologically related through endoderm-level morphogenesis. The molecular basis of cancer regularity between them involves developmental signaling pathways including HEDGEHOG, NOTCH, WNT, and CXCL12/CXCR4, an evolving genetic background, and regulatory tumor-stromal interactions. Perhaps biomarkers that explain the regularity between them have been documented - as we peruse the bioscience literature for information, we may be reading through viable biomarkers and solutions and not seeing the forest for the trees. On the other hand, perhaps more research is warranted to explain cancer behavior between the lung and pancreas. Observations in this review provide a framework on which to extract clues for future work regarding organ-specific metastasis between the lung and pancreas.

Keywords: cancer of unknown primary site, tumor dormancy, preneoplasia, seed and soil hypothesis, tumor heterogeneity, developmental signaling pathways,regulatory tumor-stromal interactions, genetic background, EMT/MET, pan-cancer analysis, diagnosed as secondary, best treatment option, molecular processes, difficult to distinguish, small cell

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Abbreviations: LC, lung cancer; NSCLC, non-small cell lung cancer; LADC, lung adenocarcinoma; SCC, squamous cell carcinoma; LCNEC, large cell neuroendocrine carcinomas; Other Type, LCC, large cell carcinomas, other type; NSCLC–ASCC, adenosquamous cell carcinoma; SCLC, small cell lung cancer; BSD, bronchial squamous dysplasia; CIS, carcinoma in situ; AAH, atypical adenomatous hyperplasia; PNCH, pulmonary neuroendocrine cell hyperplasia; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; Panin, pancreatic intraepithelial neoplasia; PMCN, mucinous cystic neoplasms; IPMN, intraductal papillary mucinous neoplasm; PNET/ICT, pancreatic neuroendocrine tumors/islet cell tumors; PACC, pancreatic acinar cell carcinoma; CUP, cancer of unknown primary site; Hh, hedgehog; EMT, epithelial to mesenchymal transition; MET, mesenchymal to epithelial transition; CTC, circulating tumor cell; Cscs, cancer stem cells; HNC, head and neck cancer; Goqs, guiding observational questions

Introduction

Lung cancer (LC) remains the number one cause of cancer death in the United States (US) and the world, with an expectation of 222,500 new cases and 155,870 deaths in the US in 2017.[1] About 80% of LC deaths in the US are caused by smoking, but trends are declining, as falling mortality rates reflect smoking reduction.[2,3] LC is often diagnosed at advanced metastatic stage, and is expected to remain the leading cancer killer beyond the year 2030.[1,3,4] Meanwhile, pancreatic cancer (PC) is expected to be the 3rd leading cause of cancer-related death in the US in 2017, and like LC, risk is significantly increased in smokers compared to never smokers.[1,2] There will be 53,670 new PC cases and 43,090 deaths in the US in 2017.[1] Most alarming is that PC is expected to become the second leading cause of cancer death by 2030, surpassing colorectal cancer.[1,3] Although survival rates have improved for several cancers, the same is not true for PC. Overall survival (OS) remains dismal for PC patients treated by surgery, and like LC patients, they often succumb to metastatic disease.[3,5,6] Surgery is the best treatment option in most cases, but most patients do not qualify for surgery. Without surgery, the OS rate is 3-6months.[7] Surgery alone is not curbing mortality trends, and the median OS rate of resected patients receiving adjuvant chemotherapy and/or radiation therapy after surgery is only 20-23 months.[8] Taken together, over half of all LC and PC cases are diagnosed at a distant stage, for which 5-year survival rates are a dismal 4% and 2%, respectively.[2] These data suggest that molecular research, and randomized and blinded clinical trials that focus on prevention and early-stage detection, and advanced-stage molecular therapy, must be continued.[9,10]

Cancer behavior refers to variations in growth, malignant progression, and morbid systemic spread of tumors, through wide-ranging degrees of severity.[11,12] The totality of biological properties that explain these events include but are not limited to: mutations,

genetic background, signaling pathway redundancy, pathway interactions (epistasis), gene pleiotropy, tumor-stromal interactions (TSIs), epithelial-to-mesenchymal (EMT) processes, tumor dormancy, angiogenesis, and histological subtype.[13,14] Cancer behavior can range on a continuum from benign/indolent to aggressively metastatic.[15–17] Biological mechanisms that explain variations in cancer behavior are not completely known.[12]

Molecular biology and (sometimes) organ specificity determine where a tumor spreads (if it spreads at all) and the ensuing severity of metastasis.[12] Sometimes metastasis is undetectable, asymptomatic, and discovered incidentally-also known as "occult metastasis"-or it is discovered in recurrent assessments or autopsy.[18] Sometimes metastasis is diagnosed as secondary cancer of unknown primary (CUP), also known as "occult cancer".[19,20] Determination of the unknown primary site is often a critical challenge for clinicians. CUP is expected to be the 4th most common cause of cancer death in the U.S. in 2017, and although trends are decreasing, there are not many recent reports that specifically examine cancer biology leading up to CUP to reflect this trend, while diagnoses remain inconsistent, and prognoses mixed.[1,21,22] At autopsy, CUPs are determined to originate from a primary LC or PC in most cases.[23–24] Sometimes CUPs develop from dormancy or growth regression of primaries.[23,24] CUP patients often do not respond to adjuvant therapy, and cancer stem cells (CSCs) are believed responsible.[24] As discussed in this review, CSCs are being researched as targets for therapy regarding proliferation, dissemination potential, and organ-specific metastasis.[25]

Complications due to metastatic disease and resistance to therapy are the common cause of death in LC and PC patients.[26–29] LC and PC primaries metastasize to organ-specific sites more frequently than other systemic locations.[11,12,30,31] Interpatient heterogeneity shows that there is regularity in metastasis between the organs of these diseases. The most frequent sites of metastasis for primary LC are the adrenal glands, bone, and liver.[12,32] Metastases to the pancreas are extremely rare for all primaries at 1-2% and usually metachronous.[32] Surveys on this topic varied, but of all primary cancers that metastasize to the pancreas, LC and renal cell carcinoma were found among the most common (as references indicate, there are conflicting data in the literature regarding LC metastasis to the pancreas).[27,31–34] Small cell lung cancer (SCLC) is the subtype that frequently metastasizes to the pancreas, however, primary non-small cell lung cancer (NSCLC) subtypes also metastasize to this organ.[33] NSCLCs are divided into five different subtypes, all of which are prone to disseminate disease: lung adenocarcinoma (LADC), squamous cell carcinoma (SCC), adenosquamous cell carcinoma (ASCC), large cell carcinoma (LCC), and large cell neuroendocrine carcinoma (LCNEC).[35] The oncogenic drivers that cause migration of SCLCs and NSCLCs to the pancreas are not fully understood. Conversely, the aggressive behavior of PC appears to be related to either early dissemination, late diagnosis, or a combination of the two.[6,15,36,37] PC dissemination generally shows up in the liver, but can escape the liver and migrate to the lung, which is a common metastatic site for PC.[6,12,27] Pancreatic adenocarcinoma (PDAC), pancreatic acinar cell carcinoma (PACC), and pancreatic neuroendocrine tumor (PNET) subtypes are aggressive to varying degrees and capable of widespread dissemination, but PDAC is the subtype often presented in lung metastasis.[38] Secondary PDACs in the lung are difficult to distinguish from primary LCs because localization occurs along the alveoli, features a mucinous-type epithelium, and mimics primary bronchioloalveolar carcinoma.[27,38] Likewise, secondary lesions to the pancreas are difficult to distinguish from primary PC.[34,39] For PC patients, lung metastases offer a survival advantage over other metastatic sites, but no molecular basis has been put forth that explains this phenomenon.[39–41] There are no reports that indicate that the reverse is true - that pancreatic metastases from the lung offer a survival advantage over other metastatic sites for LC patients. These data suggest that the molecular processes that drive metastasis between these organs may have something to do with recapitulations of developmental signaling, and the fact that the organs are related through endoderm-level morphogenesis, of which Sonic Hedgehog (Hh), NOTCH, WNT, and CXCR4 are essential players.[6,42–45]

Early tumor cell dissemination is believed to involve processes taking affect in preneoplastic, benign/indolent subtypes, including bronchial squamous dysplasia (BSD) carcinoma in situ (CIS), atypical adenomatous hyperplasia (AAH), and pulmonary neuroendocrine cell hyperplasia (PNCH) in the lung, and pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasms (MCN), and intraductal papillary mucinous neoplasm (IPMN) in the pancreas.[46–48] These preneoplastic subtypes feature biological mechanisms that can drive forward metastasis before malignant invasion.[49–52] Tumor progression processes in preneoplasia alter, transform, and diversify phenotypes, but are not completely understood.[27,53–55] Pipinikas et al.,[56] showed that in situ precursory cells that are clonally related can physically migrate over distances, suggesting that multifocal preinvasive lesions in the progression from BSD to SCC originate from a common clonal ancestor, which endorses the field cancerization hypothesis of lung tumorigenesis.[56] Yachida et al.,[57] showed that PCs contain heterogeneous mixtures of subclones and each subclone contains millions of cells. The subclones are genetically evolved from the parental, non-metastatic clone, and are capable of metastasis. However, no molecular drivers were unveiled.[57] These data suggest that clonally-regulated stem and progenitor cells, and microenvironmental processes in preneoplasia and early neoplasia, are involved in dissemination and metastasis in LC and PC.[23,24,58–60] Perhaps preneoplastic dissemination signals, and TSIs in the secondary organ conduce selective growth in the new microenvironment, and these effects along with genetic background, infringe on tumor indolency, dormancy, and metastatic CUP cases.[24,61,62] Molecular profiling of TSIs may offer the possibility of screening and early detection and lead to improved diagnostics[23,62–64]

An understanding of what is going on similarly and differently between metastatic LC and PC may help explain variations in cancer biology.[31,32,33,27,34] It should be noted that all cancers acquire a similar set of capabilities necessary to manifest malignant disease. These general hallmarks of cancer were depicted in the classic article by Hanahan and Weinberg.[65] Although at advanced stage neoplasia has disseminated to various locations in most cases, metastases to the pancreas, and to the lung, are frequently originated from one to the other respective organ, which merits some investigative attention.[6,31,32,27,34,28] What are the greater molecular details that explain how and why this happens[66–69] The guiding observational questions (GOQs) are:

I. Is there robust regularity in molecular processes that specify metastasis between the lung and pancreas? Are the drivers consistent? What biomarkers can be tested?

II. What mechanisms confer resistance to secondary pancreatic lesions, making metastasis rare at 1-2% in clinical cases, and up to 11% at autopsy[34] How are the mechanisms perturbed to allow frequential metastasis from LC primaries, and, what drives the perturbation?

III. Conversely, what biological processes in pancreatic primaries prompt metastatic spread to lung to a significantly higher degree at 45%, when, as just stated, the reciprocal is seen in rare cases? What are the drivers behind these processes?

IV. Altered processes in pancreatic preneoplasias mediate succession toward ductal, neuroendocrine, and acinar carcinomas, sometimes in extremely rare performance.[70] Likewise, preneoplasias in the lung spur malignant invasion, and may prompt cancerization, sometimes in extremely rare performance.[71–74] Are the isolated molecular processions repeated upon dissemination to spur metastasis? Are we in fact looking at reiterations that drive recurrence and metastasis between the two organs[8,11,67] Are these the same processes that give rise to CUPs[11,24] Do these processes interplay with tumor dormancy, the dormancy-to-proliferation switch, regression of primaries, and CSC plasticity.[16,75]

These GOQs establish the basis for this review, and designate origination of disease as an essential premise. Hypothetically, there are undetermined tumorigenic processes - biomarkers - in action that explain contrasting LC and PC behavior.[6] On one hand, molecular processes resist secondary pancreatic metastases at a low occurrence of 1-2%, yet exhibit frequent organ-specific metastasis from LC primaries[30,31,33,27,34] On the other hand, molecular drivers promote sensitivity to lung metastases from pancreatic primaries at a much higher occurrence rate of about 45%.[27] Determining the molecular signatures could clarify contradistinctions in LC and PC metastasis, and lead to biomarkers that guide the engineering of personalized drugs.

Molecular connections between Lc and Pc

Recapitulated developmental signaling implicated in cancer behavior: Based on interpatient heterogeneity, the molecular basis of cancer regularity must be considered for effective personalized therapeutics. Signaling pathways and TSIs are directed by genetic background (reviewed in the next section) to conduce subtype-specific and organ-specific lung and pancreatic neoplasia.[76–79] Evidence shows that developmental signaling pathways that function most prominently in embryogenesis are aberrantly activated in neoplasia, recapitulating processes that drive development.[80] Not only are Hh, NOTCH, WNT, and CXCR4 involved in endoderm-level development, they are also active in preneoplastic signaling, CSC activation, locoregional and disseminated tumor progression, and metastasis.[80–85] There are inhibitors for these pathways, some are approved by U.S. Food and Drug Administration, and more are being tested.[86] However, drug resistance frequently occurs in LC and PC cases, and there are no standout reports examining developmental signaling to explain subtype-specific and organ-specific metastatic behavior between the lung and pancreas. Described here are Hh, NOTCH, WNT, and CXCR4, and their roles in LC and PC biologic behavior.

Hh signaling is virtually inactive in adults except for tissue repair and maintenance functions. Aberrant reactivation of Hh signaling is long known to play a role in lung and pancreatic tumorigenesis throughout the continuum from preneoplasia to metastasis, in a subtype specific manner.[27,87,88] Watkins et al.,[87] reported that Hh signaling activates lung neuroendocrine progenitor cells in the same way it functions in the maintenance and progression of SCLC.[87] Under conditions of cellular stress, such as through drug intervention, the Hh pathway helps maintain cellular survival, growth and invasiveness, and thwarts cell destruction by signaling for effectors that stimulate drug resistance. Lin and colleagues examined the functions of Hh signaling in LDAC cells with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs).[88] The authors found that the Hh pathway drives cancer progression in the face of EGFR-TKI antagonism. Hh interacting protein (HHIP) is a glycoprotein that binds to Hh ligands, shutting down Hh signaling. This glycoprotein is ablated through hypermethylation in pancreatic neoplasms making Hh fully operational. Lin and colleagues confirmed that HHIP is also shutdown in LADC, and overexpression of HHIP thwarted LADC growth in mice. Thus, the investigators present evidence that Hh is implicated in driving EGFR-TKI resistance in LADCs.[88] Hao et al.,[89] also investigated oncogenic Hh signaling in PC stem cell marker expression, cellular proliferation, progressive EMT processes, and tumor cell invasion, and the pathway was shown to co-regulate these processes.[89] Hh also heavily crosstalks with the TGFβ and KRAS pathways, major players involved in tumor progression, EMT and MET processes, and metastasis.[69,75,90,89] Taken together, these data show that the Hh pathway influences cancer behavior in both LC and PC lesions.

The NOTCH pathway plays several important roles in cancer progression, and its most critical role is at the nexus between invasion and metastasis Ni et al.,[91] At this juncture, the NOTCH pathway crosstalks heavily with the EGFR pathway, and its communication is essential for reactivation of dormant CSCs and disease recurrence.[92] Exhibit in their review that NOTCH is activated in pancreatic CSCs that have survived conventional therapy Ni et al.,[91] Furthermore, NOTCH mediates pancreatic tumor relapse, and re-ignites growth and metastasis, and it does this thorough Notch-1 upregulation, induction of NF-κβ and its downstream effectors, expression of microRNAs (miRs) that regulate CSCs (miR21, miR200b, miR200c and miR34), induction of the EMT phenotype, heterogenic clonal expansion, and malignant migration Ni et al.,[91] NOTCH performs the same operations in lung CSCs - which serves as a biomarker that defines lung CSCs due to the strength of the NOTCH signaling profile. Using GFP reporter recombinants and sphere-forming assays, Hassan's group showed that NOTCH functions in heterogenic self-renewal (clonal heterogeneity). Through inoculation in mice, they also showed that NOTCH influences resistance to chemotherapy, and decreased LADC overall survival.[93] These data suggest that recapitulated signaling through NOTCH is a vital force in LC and PC growth behaviors.

Wnt genes are downstream targets of the Hh pathway. WNT augments NOTCH signaling in tumor progression, and crosstalk frequently occurs.[94,95] Both WNT and NOTCH co-regulate CSC biology, making WNT an equipotent therapeutic target.[96,97] Interestingly, both pathways are involved in the re-vitalization of dormant cells, and recent reports reveal that turning off WNT signaling is implicated in metastatic dormancy and immune system evasion.[98–100] Pollard's review implicates that inhibition of WNT serves to activate dormant epithelial cancer cells.[99] Malladi et al.,[100] confirm Pollard's review, showing that autocrine inhibition of WNT signaling is code for evading the immune system and activating dormant tumor cells, implicating WNT inhibition in metastatic spreading.[100] These reports are counterintuitive to the report by Wang's group, who showed that inactivation of WNT through CXCL12/CXCR4 inhibits PC progression.[101] Further confoundment emerges through evidence that CXCL12/CXCR4's activation of the Hh pathway, which turns on WNT, induces invasion and EMT modulation.[102] These seeming conflicts in cancerogenicity must be clarified, and likewise, the interplay of WNT and NOTCH in tumor dormancy and metastasis also must be clarified. If by further investigation these seeming conflicts connect and are justified, then per Malladi et al.,[103] and Pollard's review, WNT's dysregulation

can only be part of the story, because the dormancy-to-proliferation switch and angiogenesis also play roles in driving metastasis.[16,103,104] As recently reviewed in Bleau and colleagues, the stroma co-regulates CSC sustenance, re-programming of the extracellular matrix, and the angiogenic switch;[105] therefore, (putative) WNT dysregulation, and regulation from the stroma, drive forward cancer progression. These findings warrant further investigation regarding the interrelationships between NOTCH signaling, WNT signaling, stromal co-regulation of CSCs, the dormancy-to-proliferation switch, and angiogenesis, which could possibly help explain aggressive cancer behavior and drug resistance.[16,25,106]

The CXCL12/CXCR4 pathway is critical for LC and PC progression, and plays a role in metastatic homing of CSCs to specific organs.[107,108] Recent reports show that it operates in stem cell niches with Hh and NOTCH in the progression of other cancers.[109,110] CXCR4 is a recognized marker for CSCs, and this pathway may control frequential dissemination of PC tumor cells to the lung, and LC tumor cells to the pancreas.[111,112] Interplay between CXCL12/CXCR4, Hh, and NOTCH may be consistent in LC and PC progression, which provides clues to GOQ-1. Furthermore, the CXCL12/CXCR4 pathway interacts with the stroma to influence neoplastic extravasation and the metastatic cascade.[113] It also co-regulates immunosuppressive mechanisms.[114,115] Pathway ligands are as critical as the CXCR4 receptor, as they can transduce signals through receptors other than CXCR4, driving oncogenic mechanisms through several pathways.[116] For example, CXCL12 can bind to CXCR4 or CXCR7 to induce similar oncogenic mechanisms. Likewise, macrophage migration inhibitory factor (MIF) is an alternative ligand that can bind both CXCR4 and CXCR7 in place of CXCL12.[117] Strikingly, THE CXCL12/CXCR4 pathway has not been studied extensively in a subtype-specific manner in preneoplastic lung and pancreatic lesions, such as BSD, CIS, AAH, PNCH, MCN, and IPMN.[118] Kure et al.,[119] reported a comparative study of CSC markers in PanIN-1, PanIN-2, and PanIN-3 vs. PDAC.[119] Using patient-derived paraffin-embedded tissue, the investigators exhibited that both CXCR4 and epithelial-specific antigen (ESA), two proven morphoregulatory CSC markers, increased expression in the PanIN-to-PDAC progression. ESA displayed significant increases beginning at PanIN-1, and CXCR4 displayed significant increases beginning at PanIN-2. All CSC markers analyzed in the report were expressed in all stages of the progression. This suggests that upregulated CXCR4 expression in preneoplastic PanIN is indicative of proliferation, onset of migration, and metastasis, as they indicate in PDAC cells, making CXCR4 and its peripheral effectors of the chemokine-receptor network attractive biomarkers.[119]

Targeting intratumoral pathways has not been enough to curb LC and PC disease outcomes despite outstanding research.[25] For example, targeting NOTCH alone may not be enough to abrogate drug resistance, as it has been shown that drug inhibition of NOTCH may induce squamous epithelial malignancies.[120] The WNT pathway is fickle, and may prove unreliable as an isolated target aimed at alone. Whether WNT is inhibited or activated cancer progression ensues.[84,95,97–100] For example, SOX9 regulates the WNT pathway. One of WNT's downstream targets is osteopontin (OPN), but the FGF pathway can alternatively activate OPN. If SOX9 or the WNT pathway are ablated, OPN can still be expressed as a downstream target of the FGF pathway - an exhibition of functional redundancy. Fully knowing regulatory mechanisms regarding the WNT pathway is not enough to stop OPN expression. Similar examples can be cited for Hh and CXCR4 pathways. This suggests that genetic background directs differences in cancer behavior and treatment response (Table 1).

Genetic background: redundancy, epistasis, and pleiotropy in cancer behavior: Genetic background regulates recapitulated developmental signaling, and for this reason, combination therapy (a drug cocktail approach) is being researched as a treatment modality.[66,121,122] Genetic background refers to the genomic and epigenomic landscapes that code for the molecular biology and survival mechanisms of the cell.[61,123] All cancers feature a mutator phenotype, and the genetic background evolves through genomic instability and gradual widespread mutations.[124,125] In sporadic cancer cases, genomic instability is often acquired by risk factors such as smoking.[126,127] In heritable cases, genomic instability is prompted by inborn mutations, similar to acquired mutations in sporadic cases. The difference is that the molecular basis of heritable carcinogenesis is associated with predisposition and probability by family history, with disease being presented earlier, which further affirms genetic background as the producer of cancerogenicity.[20,128–130]

There are cases where cancer was diagnosed as sporadic, although there was a heritable predisposition featured.[131] Such cases relate to Dr. Alfred Knudson's two-hit hypothesis.[132] In heritable cases, the two-hit hypothesis refers to loss of heterozygosity (LOH); inactivation of both alleles of an oncogene (OG) or tumor suppressor gene (TSG) through inherited germline mutation(s) in one allele as the "first hit", and subsequent mutation(s) in the second allele (owing to genomic instability) as a "second hit". In sporadic cases, both hits are acquired on an OG or TSG as somatic mutations.[132] Germline haploinsufficiency in the background of somatic mutation(s) can influence sporadic oncogenesis.[133,134] Recalling GOQ-4, it is quite possible that haploinsufficiencies influence sporadic CUP, rare cancer, and metastatic-like cancer cases, such as reported by Newman and colleagues, and Dr. Killen, respectively.[11,70,73] Haploinsufficiencies among miR genes could predispose family members to heritable cancer, and influence oncogenesis and metastasis in sporadic cancer.[135] These examples are digressions from Knudson's two-hit hypothesis. Investigations that examine genetic background effects on heritable and sporadic cancer are warranted to generate specialized therapeutic approaches.

Genetic background effects also relate to the seed and soil hypothesis formulated by Dr. Stephen Paget.[136] The seed and soil hypothesis refers to tumor cells that exhibit patterned migration and metastatic colonization in site-specific organs through premetastatic niche preparation.[136] Lung metastasis is a common secondary incidence for known primaries, and this was thought to occur through cancer cells being trapped in pulmonary microvessels. Evidence suggests that a premetastatic niche is formed before arrival of lung CSCs, but how premetastatic niches are formed is still being investigated.[137] Recent evidence suggests that exosomal content dispersion via tumor-released exosomes into blood circulation is implicated in preparing the premetastatic niche and immunosuppression.[138] While the seed and soil hypothesis is robust in conceptualizing organ-specific metastasis, and is much appreciated regarding Dr. Paget's intellectual insights, it is still hypothetical and subject to inspection. Metastasis in general is not completely understood.[139] Disseminated tumor cells can become attached through cell surface adherence or microvessel size restrictions.[139] Adhesive components on tumor cells (e.g., EpCAMs, integrins, glycolipids, etc.) can adhere to microvessel endothelial cells, subendothelial basement membrane matrix, and parenchymal cells.[30,28,139,140] That being said, premetastatic niche is thought to not be causal in all metastatic cases.[140,141] Recalling GOQ-2 and GOQ-3, genetic background likely plays a significant role in organ-specific LC and PC metastasis. If susceptibility to cancer incidence is increased through pathogenic germline mutations in lung and pancreatic cancer

cells (seeds), then it seems plausible that stromal gene expression subsequently evolves in the invaded microenvironment (soil) to meet the survival needs of predisposed cells, especially where those cells are capable of adhering.[142] It only takes one precancerous (founder) cell to initiate cancer, recurrence, or metastasis.[143] In contrast to the seed and soil hypothesis, site-selective adhesion and genetic background might partly explain germline and sporadic rare metastases, including those presented in the pancreas.[144,145] Recalling GOQ-1, pre-programmed CSCs may succeed through premetastatic niche or site-selective adhesion mechanisms, suggesting that the molecular processes in LC and PC metastasis are probably variable and inconsistent, and relevant biomarkers transiently change (as thought to happen in drug resistance), although interpatient regularity is clinically observed.[12,28,110,114,143] Randomness with outcome regularity is evident through the recent findings by Martinez and colleagues that intratumor heterogeneity mimics intertumor heterogeneity.[146] Investigations are needed to differentiate site-selective adhesion and premetastatic niche processes in metastasis. Moreover, rigorous testing of the two-hit and seed and soil hypotheses are warranted to further elucidate the genetic background impact on oncogenesis, and better potentiate individualized therapy approaches.[81,147,148]

Genetic background also impacts clonal diversity through parallel progression.[11,28,125,149] The parallel progression model affirms that cancer behavior is largely due to genetic background; it is the accepted model to track cancer cells of origin. Evidence from this model serves as a paradigm shift from the former serial progression model.[149] Observed features that endorse parallel progression are depicted in CUPs, variations in latency, and cases of metastasis of metastasis (intermetastatic heterogeneity).[28,146] Although reports present evidence, pathway involvement in clonal origination is difficult to trace.[150,151] It is not known whether a founder host stem cell, or induced cancerous cell that acquires stemness, originates oncogenesis.[27,104,121,143] This is important because mutations produce detectable tumors on a time scale ranging from months to dozens of years, depending on background influences on tumor-stromal interplay.[27,75,99,100,125,152,153] On one hand, metastatic CSCs originate from mutations in normal host stem cells through a process referred to as "pretumor progression".[150] On the other hand, invasive cancerous cells acquire a stem-like phenotype and then originate metastasis.[27,104,143,150] Research must determine what driver mutations in cells of origin contribute to cancer cell fate and behavior.[24,25,154,76,123,154] Validating background effects on cancerogenicity through redundant, interactive, and pleiotropic connections across the tumor-stromal axis could lead to effective therapeutic approaches.[153,154]

Genetic redundancy refers to paralogous genes that produce the same phenotype.[155] Paralogous genes that functionally compensate one another implies their importance to cell survival, and fortifies Darwinian selection by reproductive fitness.[155,156] Genetic redundancy does not necessarily imply functional redundancy, as paralogous gene products may have divergent functions elsewhere in the cell (e.g., moonlighting proteins).[156–158] The crosstalks of Hh, NOTCH, WNT and CXCR4 functionally succeed in proliferation of cancer phenotypes and variations thereof.[80,159] Indeed, this is what we see in acquired and intrinsic drug resistance. Despite treatment with pathway inhibitors, LC and PC phenotypes and variations thereof continue to progress and metastasize.[80,160] The 'synthetic lethality' approach aims to thwart oncogene addiction and pan-resistance - fortified disease progression through the exploits of functional redundancy.[157,160] For example, CXCR4, NOTCH, and WNT pathways can turn on Hh downstream targets. If Hh is ablated, its downstream targets can still be expressed through crosstalks.[147] Likewise, the Hh pathway crosstalks with other pathways such as TGFβ and IGF-R. If TGFβ and IGF-R pathways are abrogated, their downstream targets are still activated by Hh.[160,161] Thus, genetic redundancy fortifies natural selection for cell survival (drug resistance).[162] Combination therapy and synthetic lethality strategies are currently being explored to transform cancer phenotypes to lethal (apoptotic) phenotypes.[66,157,160,162] Genetic background assessments on a case-by-case basis may improve clinical efficacy in such pursuits. The impact of epistasis regarding combination therapy and synthetic lethality should also be considered.

Genetic epistasis refers to gene-gene interactions that diversify cellular phenotypes, creating an assortment of cellular properties along the continuum of clonal expansion.[55,163,164] Genomic instability alters the network of gene interactions during tumor progression, making epistasis an evolutionary process.[98,165] Genetic epistasis and host immunosurveillance are responsible for inefficiency of metastatic colonization, where thousands of cells disseminate but only a rare few survive the metastatic cascade.[16,166] Epistasis may also be an essential factor in the dormancy-to-proliferation switch, reactivating tumor dormancy.[16] As mutations increase during cell transformation from normal to cancerous, gene interactions across the tumor-stromal axis evolve to maintain cell survival.[150,163,165,166] Interactions that abrogate immunomodulation of the metastatic process in immunotherapy is not understood.[16] Growing tumors adapt to microenvironmental changes during immunotherapy, and evolving interactions across the tumor-stromal axis prepare tumor cells for immunotherapeutic escape.[167] This might happen through development of compound haploinsufficiencies, such as through SNPs and chromosomal microdeletions, which can be difficult to detect.[135,168,169] For instance, regulatory T cells (Tregs) are immunosuppressive, and effector T cells (Teffs) are immunostimulatory. Tumor cells that recruit and respond to Teffs may succumb to anti-tumor immune responses, whereas tumor cells that recruit Tregs may prevail in their immunoescape.[167] Treg recruitment may occur through unsuspecting mutation-induced compound haploinsufficiencies that suppress Teff recruitment and alter TSIs. Perhaps if such an "interactive switch" did not occur, immunoresponsiveness would prevail. Mutations endow reproductive fitness, and as a mutator phenotype, tumor cells might be able to force stabilized evolution through mutations to avert cell death. Much is still unknown, and nothing is conclusive. Recalling GOQ-1, the robust regularity that we see in LC and PC interpatient heterogeneity is the ability of cancerous cells to change epistatically without compromising survival.[170] Thus, epistasis is a powerful force in cancer evolution.

Signaling pathway crosstalk is as much a form of epistasis as it is a form of functional redundancy. Tumor dormancy, and the seed and soil hypothesis, feature this integration of concepts. Dormancy is thought to occur by the seed and soil process in some cases, particularly in cases of immunosuppression and therapeutic resistance.[16,28,75,171] The lynchpin is pathway crosstalk interactions across the tumor-stromal axis. Co-evolution of tumor and stromal cells occurs by interactions that constitutively evolve (epistasis) and constitutively signal (redundancy) along the progression continuum, inducing reactivation from dormancy.[16,25,28,75,163,172] Intertumoral heterogeneity exhibits regularity by the evolving molecular interactions and changeful signaling pathways that occur across the tumor-stromal axis, case by case.[123,173-176] Tumors harbor malignant cells with the evolvability of surviving the host immune response, metastatic cascade, and tumor dormancy.[68] In every individual case, we observe cells attempting to survive, creating wounds that never heal. Tumor-stromal regulation must be unraveled to determine biomarkers that direct cancer cell evolution towards cell death, as depicted in spontaneous regression.[167,177]

Gene pleiotropy is also a factor in producing diverse cancer phenotypes. Gene pleiotropy refers to the influence of a gene (or pathway) on multiple phenotypic properties and mechanisms.[178] Like redundancy and epistasis, gene pleiotropy significantly influences cancer behavior. From the stromal perspective, one of the biggest concerns about gene pleiotropy relates to chemokine and cytokine biology. Many chemokines and cytokines are characteristically pleiotropic.[111,178–182] Pleiotropic effects induce immunosuppression in the stroma, and increase phenotypic change in tumor cells at the invasion front.[178,183] Mutations such as SNPs, microdeletions, microinsertions, and chromosomal rearrangements can induce pleiotropic effects in LC cells, which, in turn, destabilize phenotypic stability in stromal cells, and affects immunotherapeutic treatment.[184] From the tumor perspective, pleiotropism triggers CSCs and other cancerous cells endowed with molecular fitness primed for evolvability toward the furtherance of disease - this is exhibited in the WNT signaling pathway.[185] Aside from pleiotropy, tumor cell production of chemokines and cytokines also exhibit functional redundancy, which exacerbates the molecular complexity of tumor progression.[181,182] Downregulation of a pleiotropic chemokine receptor, such as CXCR4, can produce phenotypic changes in an epithelial cancer cell without affecting its survival and progression potential. CXCR4 is implicated in numerous processes that cross between pleiotropy and redundancy, which serve to sustain, clone, and diversify cellular phenotypes. These molecular properties may justify why downregulation of CXCR4 impacts tumor dormancy.[186,187] Several WNT target genes, such as IL-8, SOX9, CD44, AXIN2, MMP7, VEGF, and TDGF-1, exemplify, or are affected by genetic pleiotropy and redundancy. Some of these actions affect the cell cycle, cytoskeleton proteins, matrix metalloproteinases, and cell-matrix interactions.[188–193] Therefore, WNT pathway upregulation, downregulation, or abrogation through canonical and non-canonical channels significantly affects clonal diversity and cancer behavior.[190] The Hh pathway (and NOTCH) may exhibit similar properties to the WNT pathway in LC and PC metastasis, through the targeting of VEGF, although the pathways present different gene targeting programs.[194,195] For example, downstream Hh/Gli target genes such as FOXM1, TWIST2, ZEB1, ZEB2, VEGF, Ang2, and BMP4 have pleiotropic and redundancy characteristics like WNT, imposing on cell proliferation, decreased apoptosis, and metastasis; however, this is a different gene targeting program from the WNT pathway, but both pathways engage angiogenesis through VEGF.[194,196,197] Abrogation or activation of pleiotropic pathways may mediate tumor cell evolution. Considering the number of genes in the human genome, diversity seems almost limitless. Thus, gene pleiotropy, like redundancy and epistasis, has a big influence on tumor cell evolvability and metastatic potential.[150] There is also redundant pleiotropy. Exosome content dispersion, in conjunction with chemokine, cytokine, and ECM receptor signaling cascades, may produce redundant pleiotropic effects, as secreted exosomes from tumor cells may contain the same pleiotropic chemokines released from stromal cells.[198,199]

These effects - redundancy, epistasis, and pleiotropy - have thus far proven indefatigable in stopping LC and PC progression and metastasis. Recalling GOQ-2 and GOQ-3, why are LC and PC primaries metastasizing from one to the other respective organ on a frequential (regular) basis? Why do CUPs develop most often from lung and pancreatic primaries?[21–24]

Tumor heterogeneity, emt/met processes, and regulatory tsis in cancer behavior: Genetic background directs origination, clonality, and metastatic progression of LC and PC, and signaling pathways are the conduits of that directorial script.[128,147,150,200-202] Stochastic variations in SNPs, genomic rearrangements, epigenetic alterations, LOH, haploinsufficiency, and so forth, are thought to influence tumor heterogeneity and interpatient regularity.[203] Hh, NOTCH, WNT, and CXCR4/CXCL12 transmute genomic and epigenomic programming into actionable tumor progression.[121,161,204-207] Without an understanding of the divergent molecular TSIs that impose on cancer behavior, a one-size-fits-all therapeutic approach in treating LC and PC patients has a inherent probability of failure.[208–210] Analyses regarding genetic background should be considered in the context of tissue specificity, as some mutations may generate different phenotypes in different anatomic sites of human body.[165,211,212] Genetic background in epithelial tumor cells contains only part of the explanation for tumor heterogeneity and cancer behavior. Genetic background in stromal cells also has a big influence, suggesting that TSIs are uniformly regulatory in cancer behavior.[17,62,67,75,213] Regulatory biomarkers are localized throughout the neoplastic microenvironment and are induced by genetic background cues in tumor cells and stromal cells.[67,81,84,150,151,213–218] The invasive front serves as the junction for regulatory TSIs. Examination of genetic background and intercellular signaling may unveil regulatory biomarkers that regard GOQ-2 and GOQ-3. Tumor invasion is variably dynamic and thought to occur by EMT processes in some contexts.[204,219–223] However, the EMT is not the only program for tumor invasion.

The EMT is a conserved process that occurs primarily in human embryogenesis. It is a well-documented process in development and disease.[17,42,206,222,224] The EMT is defined by a three-fold classification scheme: Type 1 (embryogenesis, organ development), Type 2 (tissue repair, wound healing), and Type 3 (loss of cell-cell adhesion and apical-basal cell polarity in tumor progression).[222] During Type 3 EMT, cancerous cells dedifferentiate into CSCs, and transdifferentiate into mesenchymal-like stromal cells, jointly invading the stroma, and promoting dissemination and metastasis. MET is the reversal of these conversions at metastatic sites after dissemination.[225,226] Changes in epithelial, mesenchymal and intermediary biomarkers, e.g., cell-cell junctions, serve to confirm the validity of EMT.[204,224] However, amoeboid invasion, coordinated collective invasion, and cohort invasion are other programs for tumor cell invasion and tissue remodeling aside from EMT.[204,223] The genetic basis of tumor invasion is questionable, and the EMT must be validated as to when it does and does not occur - that is to say, when it is and is not capable of occurring.[53, 206,227–230] Essentially, incongruence between the EMT process and clinical interpretation of disease course justifies the study of plasticity and genetic background in lung and pancreatic preneoplasias. If drivers can induce epithelial cancerous cells to disseminate from preneoplasias, then the genetic background capable of programming stemness and dissemination from the preinvasive stage, as opposed to an EMT program, is highly intriguing.[231,235]

Reports show that the EMT process conduces tumor heterogeneity.[159,206,236,237] Tumor budding and clonal diversion occurs at the invasive front through dedifferentiation and transdifferentiation of epithelial cells, which is partly where the controversy about EMT lies.[152,238] Regulatory pathway interactions in clonal heterogeneity and plasticity is not completely understood. Distinguishing EMT-type tumor cells from mesenchymal stromal cells at the invasive front is enigmatic, and may require elucidation of pathway interactions to differentiate them, as they have similar morphological and marker characteristics.[227,237] Hh, NOTCH and WNT pathways are the channels that communicate tumor invasion in the EMT process. Hh and NOTCH promote E-cadherin decreases, resulting in loss of cell adhesion, and motility.[221] WNT plays a critical role between tumor and stroma by initiating tumor budding and driving PC cell

stemness.[152,238] During tumor budding processes, EMT-type cells become mesenchymal-like.[152,238–240] CSCs and EMT-type cells have similar properties, proliferate heterogenically at the invasive front, and form a stem cell niche with stromal components.[14,110,137,152,165,241] EMT-type cells do not proliferate during invasion, but may be triggered to transdifferentiate for proliferation.[152] The Hh pathway also plays a role in driving forward hypoxia-induced EMT processes.[242] Hypoxia and metabolic stress (nutrient deprivation) induce the stem cell niche to initiate tumor invasion and drug resistance through tumor-stromal paracrine signaling.[110, 159,220,237,241,243–245]

Hypoxia refers to deficient oxygen (O2) levels that are lower than normal in tissue (pO2 < 30mmHg).[246,247] Reduction of O2 levels in tumors occurs by heterogenic tumor proliferation.[248,249] Hypoxia is a kind of signaling pathway that prompts HIF-1 to induce stromal mesenchymal cells to secrete lysyl oxidase (LOX), which signals tumor cells to undergo dedifferentiation to CSCs, and mediates bone marrow progenitor cell recruitment at premetastatic niches for metastasis.[137,221,247,250,251] Detached tumor cells likely divert from this program when there is no premetastatic niche conducive for survival.[138,252] Hypoxia also induces angiogenesis through HIF-1 activation of VEGF, and again, tumor cells likely divert from this hypoxia-driven program in cases of tumor and angiogenic dormancy.[75,252] Metabolic stress imposes similar dysfunctions. Genetic instability and acidification of the stroma through the Warburg Effect severely stress the metabolic machinery of tumor cells, driving HIF-1 induced survival mechanisms.[244,249] Interactive pathways become engaged in the evasion of apoptosis. Tumor cells interact with extracellular matrix (ECM) and stromal effectors through chemokine, cytokine, and ECM receptors.[254,255] Stromal signaling cascades crosstalk with tumor signaling pathways and their effectors during EMT, including NOTCH, WNT, and CXCR4, as tumor cells attempt to evade apoptosis.[255–259]

EMT reversal is thought to play a role in completing metastasis.[260] Although less is known about the MET process, there is convincing evidence regarding its concept. After EMT, intravasation, dissemination, extravasation, and metastatic colonization in secondary organs, heterogenic growth begins (after a period of dormancy). After dormancy, the MET process begins, as morphohistological characteristics dedifferentiate backwards from CSCs to epithelial cancer cells.[250,260] Recalling, GOQ-4, eventually MET lesions gain rudimentary vasculature through angiogenesis and a desmoplastic stroma, recapitulating their primaries anew - which could be important features in tracking CUPs.[67,261] Critical aspects about the MET process are receptor biomarkers, changeful interactions that accompany those biomarkers, and de novo, unique mechanisms that occur in the MET process.[262] Developmental signaling pathways also play a role in the MET-metastatic process. Upregulation of the NOTCH pathway is implicated in conversion (EMT), whereas downregulation of the NOTCH pathway is implicated in reversion (MET).[91,93,263] The WNT pathway is a known "double inducer" that drives EMT at the primary invasive front, and MET in metastasis.[260] CXCR4/CXCL12 knockdown inhibits angiogenesis.[264] These examples exhibit the essentiality of recapitulated developmental signaling in MET-metastatic processes. Therefore, further investigating these pathways regarding the differentiable molecular genetics controlling EMT, and MET, should be considered.

The common thread linking tumor heterogeneity, EMT/MET, and metastasis is regulatory TSIs. It is long known, as Hanahan and Weinberg pointed out, that homeostatic "gatekeeper" regulation (apoptosis-driven) and cell-adhesion regulation (anti-invasion-driven) are jointly compromised as cancer hallmarks.[65] Hypoxia inducement of EMT somehow diverts homeostatic TSI regulation, and the question remains, "where is the connection?" [265] Furthermore, in single epithelial tumor cell dissemination, the hypoxia inducement program is likely not employed in cases of dormancy, reactivation, proliferation, and metastasis.[266–269] Perhaps a pan-cancer expression profiling approach (reviewed in the next section) can provide some clues as to how hypoxia and metabolic stress variably drive dysregulation of cell adhesion and apoptosis, and, how a singly disseminated epithelial cancer cell induces dormancy, reactivation, and metastasis.[270,271] As it stands, the molecular basis of TSI regulation is not completely understood.[173] Respecting genetic background, tumor cell pathway interactions with stromal regulation may help explain organ-specific metastatic behavior between the lung and pancreas.[128,272] Hh, NOTCH, WNT, CXCR4, their crosstalks, and interactions with the stroma, drive heterogenic clonality, immunosuppression, and metastasis.[14,67,224,273] Regulatory TSIs induce interactive pathways through chemokines, growth factors, ECM proteins, proteases, and protease inhibitors, among other effectors.[263,274,275]

From the stromal perspective, Hh, NOTCH, and CXCR4 are involved in immunosuppression as co-regulated by immune cells.[276–278] As described by Tlsty and Coussens, "the stroma consists of cells and connective tissue that provide contextual framework for an organ or tissue…(and) contributes to cancer development through the release of soluble mediators that regulate cell proliferation, migration, angiogenesis, tissue remodeling, metabolism, and genomic integrity".[279] The essentiality is that stromal cells regulate tumor progression with tumor cells - their reciprocal interactions are thought to work as a unified regulatory unit, as they do in development and normal tissue homeostasis. Therefore, TSIs is where genetic background is the most relevant to cellular plasticity, tumor progression, and metastasis.[128,206,250,274,279] An example of unified regulation is exemplified by the Hh pathway. The homeostatic stromal response to Hh-driven proliferation breaks tumor invasiveness, which implies that homeostatic stromal regulation is compromised in hypoxia-induced tumor invasion.[242,276] Interestingly, experimental Hh pathway ablation during oncogenesis led to depletion of stromal fibroblasts, immunosuppression, induction of EMT, and tumor invasiveness, which explains why Hh inhibitors in clinical trials don't work, and implies that the Hh pathway has some role in regulating the balance between epithelial and stromal elements.[276,280,281] The WNT pathway drives forward tumor invasion and secondary metastasis at both invasive fronts; however, fibroblast-secreted exosomes intercommunicate with the WNT pathway to conduce cell polarity for this process to occur.[198] NOTCH is involved in immunosuppression and metastatic-MET processes; however, NOTCH regulation of metastasis is induced by mesenchymal stromal cells that secrete the ligand Jagged2, which activates the NOTCH pathway, suppresses host immunity, and drives forward metastasis.[277,281,282] The CXCR4/CXCL12 pathway is a driver of VEGF-mediated angiogenesis and recruits MDSCs and Tregs in immunosuppression;[278,283] however, CXC4 and CXCL12 control of angiogenesis is regulated by cancer-associated fibroblasts that secrete IL-6 and VEGF.[284] In these examples, we observe cooperative-stromal regulation. Thus, genetic background can abrogate or alter the regulatory effects from either side of the tumor-stromal interface.

From the tumor perspective, again, tumor regulation interacts with stromal regulation, and these processes operate in unison in tumor progression. Glycolytic breakdown during nutrient depravation produces lactic acid and carbonic acid, which are released from cancer cells, creating an acidic stroma. Low pH in the stroma co-

opts the inflammatory response.[285] Dysregulation of the inflammatory response is driven by TSIs and is a cancer hallmark.[286] Tumor-released exosomes mediate stromal cell regulation of immunosuppression, angiogenesis, tumor aggressivity, and drug resistance.[197,287,288] Only a small number of studies have looked at how developmental signaling pathways in tumor cells inter-regulate with the stroma tumor-secreted exosomes [289–291]Conceptually, such interactions should not be stones left unturned in research. More work on tumor-derived exosomes regarding recapitulated signaling and TSIs, could perhaps better explain the metastatic behaviors of lung and pancreatic lesions.

Pan-Cancer analysis: Pan-cancer analysis from the cancer genome atlas (TCGA) project is a bioinformatics and omics approach that employs databases used to extract information regarding effective biomarkers and other related cancer concerns.[10,270] Used in conjunction with other technologies, assessments can unveil molecular clues about TSIs and the clonal evolution of cancerous cells. By searching for biomarkers across LC and PC subtypes, ranging in disease severity from preinvasive to aggressively metastatic, and then comparing those biomarkers through analyses with other cancers, clues could be discovered that can help explain cancer evolution and the connections between LC and PC metastatic behavior. Tumor-stromal-regulated immune responses, EMT and non-EMT tumor cell invasion, organ-specific metastases, rare metastasis, and intracellular biomarkers that mediate cancer cell evolution could also be explored. In such inquiries, stochastic similarities, dissimilarities, and patterns may be a common occurrence. The objective is to extract information regarding tumor-stromal regulation and cancer cell evolution that correlates with genomic displays across the tumor-stromal axis. Validation studies might confirm suspected biomarkers and their roles in cancer behavior, such as primary growth regression and angiogenic dormancy.

Genetic background across the tumor-stromal axis is the blueprint for cancer behavior.[219,251,292] Inquiries might include: pleiotropic pathways, genomic reconfigurations (e.g., aneuploidy, copy number variations, microinsertions, microdeletions, and translocations), genetic mutations (e.g., promoter, intronic, exonic, and splicing mutations), epigenetic alterations (e.g., de-, hyper-, and hypo-methylation, and deacetylation), epistatic genes and their interactions, diversified miR expression, EMT and non-EMT drivers of tumor invasion, autophagy and metabolism, ECM interactions, exosome-content dispersion, inflammatory mediators, stromal and ECM mediators, and angiogenic and lymphangiogenic mediators. For example, the NOTCH pathway is sometimes ablated in lung SCCs through loss-of-function mutations.[120] However, NOTCH mediates critical tumor-stromal communication.[80] Queries regarding abrogation of NOTCH, and subsequent crosstalks and genomic changes in TSIs might lead to information regarding tumor cell evolution. Inquiries can also reveal fitness and selection by determining to what degree genetic redundancy is correlated with LC and PC behavior ranging from benign (e.g., cartilaginous hamartoma [lung] and serous cystic neoplasms [pancreas]) to malignant (e.g., SCLC and PDAC). Importantly, exome inquires may not entail all clues, as intronic and intergenic mutations, for example, also impact LC and PC biology.[293,154]

Inquiries could also be augmented with proteomics and molecular biology techniques to determine if there is specified regulation, such as for exosome-content dispersion.[294] Suppression of immune cells (dendritic, NK-, and T-cells) through exosome communication plays an important role in tumor progression.[217] In the lung, immunosuppression by alveolar macrophages is a normal physiological, homeostatic function, and it must be to handle the constant onslaught of antigens through breathing.[295] Homeostatic balance between immunosuppression and immunoresponsiveness in the lung becomes dysregulated in tumor progression.[148,163]Cancer cell evolution and immune system evasion are reasons why immunotherapy is not always effective in treating LC patients, and the process is not biologically understood. In PC, TAMs are thought to be strong mediators of immunosuppression. Comparative biologic behavior across subtypes through pan-cancer, proteomics, and molecular biology analyses, among other techniques, may yield regulatory clues regarding exosome-content dispersion.

It is likely that pan-cancer analysis will be routinely used in medical treatment. Cancer behavior studies can accelerate the move forward. Memorial Sloan Kettering, for example, employs a next generation genomic sequencing test to determine if a patient's cancer carries druggable mutations, and then matches that patient to specific therapies.[296] However, even if LC or PC patients have druggable mutations, it is likely that drug resistance at some point will emerge. Other medical centers also operate genomics facilities. Cancer behavior studies may be the lynchpin that effectively integrates genomic analysis with efficacious medical treatment.

Discussion

In the pursuit to improve personalized medicine in metastatic LC and PC cases, perhaps we may not be seeing the forest for the trees. Essential molecular underpinnings may already be documented, including biomarkers in this review. Perhaps validation of research findings and formulation of remedies, although a slow process, is all that is needed to see remarkable change in LC and PC outcomes. However, if after such efforts there are still not enough biomarkers that can distinguish cancer behavior, then more work should be pinpointed in this area. Important biomarkers can emerge from organ-specific cancer behavior research. With respect to genetic background and uniform tumor-stromal regulation, biomarkers that can be exploited for efficacy is a main objective. Cancer behavior studies can capture the evolutionary underpinnings of what is presented for treatment to clinicians. Tumor-stromal regulation drives: (1) initiation toward primary tumor dormancy or indolency that remains undetectable for years; (2) dissemination of malignant cells from the primary site before localized growth, which may never become clinically detectable, causing CUPs or metastatic dormancy; and (3) localized tumor growth and progression that does not result in metastasis. For these reasons, studies that focus distinctly on cancer behavior across the full range of malignancy from preinvasion to metastasis should be carried out. Smoking reduction, for example, has resulted in declines in LC incidence; however, PC incidence has remained stagnant with a slight increase although smoking is a leading risk factor for both diseases, suggesting other inducers. Tobacco and alcohol use are high risk factors for head and neck cancer (HNC). Studies that examine benign and aggressive HNC cancer in patients who do and do not consume tobacco and alcohol may yield biomarkers. Other examples can be cited for melanoma and multiple myeloma. Dormant primary and micrometastatic tumors are commonly determined at autopsy, however, cancer behavior studies might enable clinicians to detect them in live patients. Furthermore, tumorigenic cells can disseminate during preneoplasia, but there are no validated biomarkers that indicate whether this likely has or has not occurred. Finally, primary site cancer cells can transform to dormant or indolent growth behavior before the primary site is detectable. Imaging and immunohistochemical methods determine unknown origins based on secondary malignancy, but the approach is problematic, and determinations are often arbitrarily made. Biomarkers that signify primary site (clonal origins)

are needed, which is another reason why organ-specific metastatic research must continue.[272,297,298]

Conclusion

Advances made through an understanding of LC and PC metastatic behavior would include, but are not limited to: validation of biomarkers in cancer pre-initiation, initiation, and metastatic progression; validation of biomarkers that suggest primary site location and perioperative tumor dormancy; validation of molecular signatures of cancer risk in smokers; and implementation of population-based molecular and radiologic cancer screening. The first two of this series are subjects of this review. With respect to genetic background and tumor-stromal regulation, developmental signaling pathways that partly explain LC and PC metastatic behavior have been brought to light. The Hh pathway co-regulates preneoplastic signaling toward malignancy, CSC activation, EMT mechanisms, and induces drug resistance. The NOTCH pathway co-regulates EMT progression, tumor heterogeneity, CSC dormancy and reactivation, and, it induces metastasis, disease recurrence, and resistance to chemotherapy. The WNT pathway co-regulates CSC dormancy and reactivation, EMT processes, immunosuppression, and metastasis. The CXCL12/CXCR4 pathway co-regulates organ-specific homing of CSCs, organ-specific metastasis, immunosuppression, and the metastatic cascade. Hh, NOTCH, WNT and CXCL12/CXCR4 help drive metastasis across the tumor-stromal interface. Pan-cancer technology that can be used to help elucidate LC and PC metastatic behavior has also been brought to light. Databases can be referenced in research and treatment to aid personalized treatment approaches. In closing, research that investigates organ-specific metastasis (alongside rare metastatic occurrences) is warranted to enhance resolutions regarding cancer behavior. Perhaps such investigations could bring forth biomarkers indicative of early onset, diagnosis, and prognosis. Likewise, perhaps improved personalized medicine can be realized through differentiated treatment approaches based on cancer behavior studies.

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Conflicts of interest

Author declares there are no conflicts of interest.

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