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Gene Expression Profiles and Breast Cancer Metastasis: A Genetic Perspective

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Introduction

The advent of genome wide transcription analysis has ushered in a new era in our understanding of the molecular pathology of breast cancer. Using probes immobilized on a variety of solid surfaces, investigators can now interrogate much of the genome and use the transcriptional patterns to define and categorize individual tumors. As a result, a greater understanding of the complexity and heterogeneity of the disease is rapidly emerging. “Molecular portraits”, based on gene expression profiling [1], have been identified that define breast cancer by molecular pathology, and most likely cell type of origin. Further analysis demonstrated that the molecular subclasses differed in their outcomes [2] and response to therapy in some [3] but not all analyses [4]. These “molecular portraits” have been validated across different gene expression microarray platforms by different investigators [5, 6] strongly supporting the inherent biological basis of these observations. Interestingly, although the same disease subclassifications were obtained by the various analyses, the gene expression profiles displayed little overlap [7]. A likely explanation of this observation is that the number of genes correlated with outcome is large and differences in patient populations and gene selection and filtering result in different sampling from the large core group of predictive genes [8].

Since the initial description of the “molecular portraits” in breast cancer, gene expression analysis has been avidly pursued to both refine our understanding of molecular subtypes of the disease as well as to predict patient outcome. Investigators have refined the molecular subclasses of the primary tumors by addition of a gene expression signature of wound healing [9, 10] to the initial classification to gain better discrimination of those tumors that are likely to progress. In addition, standard grading systems have been re-evaluated by the addition of molecular phenotyping to better define and refine clinical staging [11]. A significant effort has also been applied to use molecular profiling to identify patients at risk for metastatic progression. Beginning with a landmark paper in 2002 that described a 70 gene signature predictive of breast cancer metastasis [12], a number of studies have validated the original findings [13, 14] or replicated them in different patient populations and clinical settings [15–18]. The molecular phenotyping of tumors has been demonstrated to out perform current clinical parameters for predicting disease outcome [12, 14], and thus

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provides an important tool for achieving the ultimate goal of individualized therapy. Gene expression technologies are currently under development for prognostic use in the clinical setting [19, 20].

The current debate on mechanisms of metastasis

The findings described above have re-ignited a debate in the literature regarding the mechanistic origins of metastasis. The prevailing model of metastasis has been the progression model, originally proposed by Nowell [21]. This model suggests that the ability to metastasize was an acquired characteristic of tumor cells, generated by the sequential accumulation of somatic alterations as a tumor evolves. A prediction of the sequential evolution in the tumor was that only a subset of the tumor cells in the primary tumor mass would acquire all of the requisite mutational events required to activate the complete metastatic cascade, and the low probability of this occurring might therefore explain the high inefficiency of the metastatic process.

The recent microarray analysis, however, appears superficially incompatible with the progression model. The gene expression analysis has been primarily performed using bulk tumor tissue; thus the resulting gene expression profiles represent the average profile of the entire tumor. If only a subset of the primary tumor had acquired the necessary somatic alterations to progress to disseminated disease, it is unlikely that the metastatic signal would be readily discernable from the gene expression profile of the bulk, non-metastatic tissue. This has led a number of investigators to resurrect or paraphrase a theory originally proposed by Leonard Weiss [22], which suggested that the bulk of the primary tumor had the capacity to metastasize, but due to positional and/or random epigenetic events only a small fraction are capable of completing the process at a given moment in time. The major metastatic driving force of these “hard wired” tumors is thought to be the specific collections of oncogenic mutations that induce tumorigenesis [20, 23, 24]. Thus, in spite of the significant amount of tumor heterogeneity present in the tumor, on average the bulk of the tumor would be expected to display a metastatic or non-metastatic molecular profile, depending on the particular collection of causative oncogenic events.

Evidence exists to support both models. For the progression model, the existence of the metastasis suppressor genes, genes needed for regulation of growth at the secondary site but that have no effect on primary tumor kinetics, makes a strong argument for need for mutational events during metastatic progression [25]. In addition, specific gene expression patterns that mediate organ tropism have been identified in subclones of breast cancer cell lines [26, 27] demonstrating that specific molecular programs can be activated by somatic and/or epigenetic mechanisms within a subpopulation of tumor cells. For the metastatic predestination model, the phenomenon of the unknown primary cancer suggests that oncogenic mutations can directly drive tumor cells into the metastatic state. These patients, estimated at approximately 5% of cases, present with disseminated disease but have no clinically detectable primary tumor or only a small well differentiated lesion found at autopsy [28]. The lack of large primary tumor mass would militate against the necessary sequence of events predicted by the stochastically driven progression model due to lack of sufficient target tissue and presumably time to progression. Furthermore, the predestination

model makes a specific prediction about the transcriptional profiles of the primary and secondary tumors. If the metastatic capacity and the associated predictive gene expression profile were due to sequential mutational events, one would not necessarily expect that the primary tumor and its associated metastasis to have similar profiles, since the disseminated tumor would be derived entirely from a cell population that was under represented in the primary tumor. In contrast, if the same mutational events that induce the tumor also induce metastatic capacity and drive the characteristic gene expression profiles, all cells in the primary and secondary tumor would carry the same causative events. Thus it would be expected that the primary and secondary tumors would closely resemble each other transcriptionally, as has been observed [29, 30]

Genetic background plays a major role in metastasis:

Several important questions, however, currently remain unanswered. The first question is what determines metastatic potential? Is it driven primarily by somatic mutations, epigenetic events, inherited predisposition, or a combination of all three? Evidence for the first has accumulated over the past thirty or so years, and includes identification of metastasis-specific loss of heterozygosity (ex. [20, 31]) and the existence of numerous metastasis suppressor genes [32]. Epigenetic silencing has also been shown to play an important role in metastatic progression, either by silencing metastasis suppressor genes [33], or modulating transient metastatic capacity [34] by transient regulation of pro- and anti-metastatic gene expression profiles (see figure 1).

The second question is what are the underlying elements that drive the metastasis predictive gene signature profiles? The answer to this question is critical to our understanding of the mechanisms of metastasis, and also in our opinion has profound implications for the clinical application of these gene expression profiles for patient prognosis. If the metastasis predictive gene expression profiles are in fact due to the same mutations that induce tumorigenesis, as has been proposed [23, 35], then clinical prognostic tests would have to be performed using tumor tissue obtained by biopsy and/or surgical resection. This would likely require changes in clinical practice, since greater care would be required to safeguard the quality of the tissue sample to ensure adequate RNA quality and quantity for microarray analysis.

One factor that might contribute to the answer of both of these questions is the frequently under appreciated effects of genetic background. Constitutional polymorphism is responsible for much of the phenotypic variation we observe in human populations on a day-to-day basis. These polymorphisms impacts not only physiological appearance such as height, hair and skin color, eye color etc, but also can have significant impact on high penetrance Mendelian disease mutations like BRCA1 (ex. [36, 37]). Experimental evidence in mouse models has demonstrated that almost any disease state, behavior or physiological measurement tested to date has a detectable inherited component, mediated by segregating polymorphisms [38–40]. The effect of polymorphism can be observed not only at the physiological level, but at the molecular level as well. A number of studies have demonstrated that steady state mRNA levels in tissues can be significantly impacted by polymorphisms present on other chromosomes [41–44], demonstrating that gene

transcription is controlled not only by syntenic promoter and enhancer elements, but by a complex interwoven web of polymorphic cis- and trans- factors.

a) Inherited polymorphism & metastatic susceptibility

Recently, our laboratory has demonstrated that this inherited polymorphism, or genetic background, plays a significant role in determining the probability that a given tumor will progress to metastatic disease. These latest findings are based on a series of genetic mapping experiments using a highly metastatic mouse model of mammary cancer. This model, the polyoma middle-T mouse (PyMT), expresses the mouse polyoma virus middle-T antigen in the mammary epithelium of FVB/N inbred mice [45] from an early age [46], resulting in synchronously arising highly aggressive mammary tumor that metastasizes with high frequency to the lung [45]. When the PyMT mouse is bred to different inbred strains, however, significant variation in tumor characteristics are observed in the F1 progeny, including tumor latency, growth kinetics and metastatic capacity [47]. Subsequent genetic mapping experiments demonstrated that significant inherited genetic factors could be identified associated with each of these tumor characteristics [46, 48, 49], indicating that inherited polymorphism played a significant role in each of these tumor characteristics, including the propensity to metastasize.

Subsequent analysis further strengthened the evidence for the role of constitutional polymorphism in metastatic progression. Genetic and haplotype mapping were used to refine the potential candidate gene list for one of the metastasis susceptibility loci [49, 50]. Sequence analysis identified an amino acid polymorphism in a PDZ protein-protein interacting domain of the Rap1GAP molecule Sip1. Biochemical analysis revealed that the missense polymorphism present in low metastatic genotypes reduced the GTPase activity of Sip1, as well as altering the ability of the protein to bind to a known interacting protein, Aqp2. Modeling the effect of the polymorphism in a highly metastatic mammary tumor cell line demonstrated that relatively subtle variations in protein level (2–4-fold) had significant effects on the capacity of the cell line to form macroscopic lesion in the lung after subcutaneous implantation, independent of the effects on primary tumor kinetics [51].

These results were consistent with the hypothesis that polymorphism in the human population might have significant effects on the ability of breast cancer to metastasize. To more directly address this question, pilot epidemiological analysis was performed to determine whether variants in the human ortholog SIPA1 were associated with metastasis and other clinical indications of poor prognosis. As predicted by the mouse model, significant associations were in fact observed, for the presence of tumor cells in regional lymph nodes, as well as estrogen and progesterone receptor status [52]. Thus, in addition to somatic mutations and epigenetic modification, constitutional polymorphism needs to be counted in our models for metastatic progression.

b) Inherited polymorphism and gene expression profiles

Evidence that the metastasis predictive gene signature might also have a significant inherited component was again derived from our mouse experiments. Extracellular matrix genes have frequently been implicated in metastasis predictive gene signature profiles in multiple

independent studies [12, 17, 18, 53, 54] suggesting an important association of these genes with breast cancer progression. Examination of the gene expression pattern from tumors of high- or low-metastatic genotype, or tumors whose metastatic potential was suppressed pharmacologically by chronic exposure to caffeine [18], revealed differential expression of a number of extracellular matrix genes. Since the tumors in these mouse experiments were all induced by the same genetic event, namely activation of the PyMT transgene, these results suggested that the differential expression of these genes might be due primarily to inherited polymorphism rather than somatically acquired oncogenic mutations.

This hypothesis makes an important prediction. If the prognostic gene expression patterns were significantly determined by inherited polymorphisms rather than somatic mutation, then one would expect to see differential expression of these prognostic genes in normal tissue before tumor induction. Consistent with this hypothesis, quantitative RT-PCR analysis comparing normal mammary tissue from mice of two poorly metastatic genotypes versus the original highly metastatic FVB/NJ mouse demonstrated that the majority of genes from one of the metastasis-predictive gene signatures were differentially regulated between the two classes of animals [55]. It follows logically that if constitutional polymorphism is a major factor in metastatic susceptibility it should be possible to derive a prognostic signature from any tissue, rather than just tumor tissue. Using a proteomics approach to measure inheritance of salivary protein polymorphism, we demonstrated that, in the mouse at least, it was in fact possible to predict those animals destined to develop pulmonary metastasis [55], with approximately the same efficiency as was observed in the original human array experiments [12, 18].

Implications for understanding metastasis

a) Mechanism

In our estimation, these results suggest that the breast cancer microarray gene expression signatures may yield profound mechanistic insights, in addition to their already significant potential impact on clinical prognostic testing. These signatures may not be measuring only somatically induced malignant changes, but may also be measuring an underlying predisposition to metastatic disease that may be segregating within the human population. Furthermore, they have sparked a re-examination of the models of the metastatic cascade, and it least in our minds, forced the inclusion of additional variables. We are of the opinion that most of the conflicting models of metastasis can be resolved by the addition of genetic background, a factor frequently under appreciated in many of our cancer models. In this hypothesis, the probability of metastatic progression and the identity of a significant fraction of the predictive gene expression profile are established by inherited factors. As a result, the basic expression profile is present throughout the subsequently induced tumor and would be observed in spite of significant tumor heterogeneity. Somatic mutations and/or epigenetic changes that contribute to both tumor progression and the prognostic signatures would still contribute to progression, and would be superimposed on the genetic background effects. Oncogenic mutations on a highly susceptible genetic background might lead to cases of unknown primary cancers, while those on low susceptible genotypes would probably result in localized tumors (figure 2).

The role of polymorphism in determining expression levels of many genes would also help explain another observation, namely the high relatedness of primary and secondary tumor expression patterns. The hardwired theory of metastatic progression predicts that primary and metastatic tumors should be more related to each other than metastatic tumors from different patients since the matched tumors share identical or nearly identical mutation events [30]. The underlying assumption here is that the somatic mutations dominate the expression profiles. This result, however, can also be explained by inheritance of constitutional polymorphisms that regulate basal transcription rates. One would expect that the progeny of a primary tumor to look more like the tumor it arose from than metastases from other patients for the same reason that school children look more like their parents than their peers; they share a common inheritance. The differences between matched primary and secondary tumors are likely to number in the dozens to possibly hundreds due to somatic instability. The differences between tumors from individuals will not only include the different somatic variations, but also include the tens- to hundreds of thousands of difference of germline polymorphisms. As a result, it would be anticipated that tumors from an individual would look more alike than between individuals, with the possible exception of monozygotic twins.

b) Clinical implications

There are two major implications of metastasis predictive signatures derived from germline polymorphisms. First, since the polymorphisms affecting gene transcription are present throughout the body it should be theoretically possible to develop a prognostic signature from blood or some other more readily available sample than tumor tissue. Second, if the underlying polymorphisms that drive the differential gene expression can be identified, it may be possible to use DNA genotype technologies to classify patients. This may result in a cheaper, more robust clinical test due to the inherent greater stability of DNA compared to RNA, depending on the numbers of polymorphisms need to replicate the predictive power of the current microarray technologies. It is important to note, however, that these alternative strategies would not capture any portion of the predictive gene signatures that are induced by somatic mutation within the tumor epithelium. At the present time however it is unclear how much of the predictive power of these expression signatures are due to germline polymorphism or somatic mutation. Additional studies will need to be performed to address these questions, as well as to further investigate the molecular bases of these signatures and additional clinical uses. The potential to inform both mechanistic studies and clinical practice however make further investigation of the inherited components of metastasis susceptibility an exciting new avenue of research for the coming years.

References

1. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000; 406 (6797): 747–52. [PubMed: 10963602]
2. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001; 98 (19): 10869–74. [PubMed: 11553815]
3. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005; 11 (16): 5678–85. [PubMed: 16115903]

4. Sorlie T, Perou CM, Fan C, et al. Gene expression profiles do not consistently predict the clinical treatment response in locally advanced breast cancer. *Mol Cancer Ther* 2006; 5 (11): 2914–8. [PubMed: 17121939]
5. Hu Z, Fan C, Oh DS, et al. The molecular portraits of breast tumors are conserved across microarray platforms. *BMC Genomics* 2006; 7: 96. [PubMed: 16643655]
6. Calza S, Hall P, Auer G, et al. Intrinsic molecular signature of breast cancer in a population-based cohort of 412 patients. *Breast Cancer Res* 2006; 8 (4): R34. [PubMed: 16846532]
7. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med* 2006; 355 (6): 560–9. [PubMed: 16899776]
8. Ein-Dor L, Kela I, Getz G, et al. Outcome signature genes in breast cancer: is there a unique set? *Bioinformatics* 2005; 21 (2): 171–8. [PubMed: 15308542]
9. Chang HY, Sneddon JB, Alizadeh AA, et al. Gene expression signature of fibroblast serum response predicts human cancer progression: similarities between tumors and wounds. *PLoS Biol* 2004; 2 (2): E7. [PubMed: 14737219]
10. Chang HY, Nuyten DS, Sneddon JB, et al. Robustness, scalability, and integration of a wound-response gene expression signature in predicting breast cancer survival. *Proc Natl Acad Sci U S A* 2005; 102 (10): 3738–43. [PubMed: 15701700]
11. Ivshina AV, George J, Senko O, et al. Genetic reclassification of histologic grade delineates new clinical subtypes of breast cancer. *Cancer Res* 2006; 66 (21): 10292–301. [PubMed: 17079448]
12. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002; 415 (6871): 530–6. [PubMed: 11823860]
13. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst* 2006; 98 (17): 1183–92. [PubMed: 16954471]
14. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002; 347 (25): 1999–2009. [PubMed: 12490681]
15. Dai H, van't Veer L, Lamb J, et al. A cell proliferation signature is a marker of extremely poor outcome in a subpopulation of breast cancer patients. *Cancer Res* 2005; 65 (10): 4059–66. [PubMed: 15899795]
16. Foekens JA, Atkins D, Zhang Y, et al. Multicenter validation of a gene expression-based prognostic signature in lymph node-negative primary breast cancer. *J Clin Oncol* 2006; 24 (11): 1665–71. [PubMed: 16505412]
17. Ramaswamy S, Ross KN, Lander ES, et al. A molecular signature of metastasis in primary solid tumors. *Nat Genet* 2003; 33 (1): 49–54. [PubMed: 12469122]
18. Wang Y, Klijn JG, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. *Lancet* 2005; 365 (9460): 671–9. [PubMed: 15721472]
19. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. *BMC Genomics* 2006; 7: 278. [PubMed: 17074082]
20. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351 (27): 2817–26. [PubMed: 15591335]
21. Nowell PC. The clonal evolution of tumor cell populations. *Science* 1976; 194: 23–8. [PubMed: 959840]
22. Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 2001; 409 (6822): 928–33. [PubMed: 11237013]
23. Bernards R, Weinberg RA. A progression puzzle. *Nature* 2002; 418 (6900): 823. [PubMed: 12192390]
24. Weigelt B, van't Veer LJ. Hard-wired genotype in metastatic breast cancer. *Cell Cycle* 2004; 3 (6): 756–7. [PubMed: 15153810]
25. Kauffman EC, Robinson VL, Stadler WM, et al. Metastasis suppression: the evolving role of metastasis suppressor genes for regulating cancer cell growth at the secondary site. *J Urol* 2003; 169 (3): 1122–33. [PubMed: 12576866]

26. Kang Y, Siegel PM, Shu W, et al. A multigenic program mediating breast cancer metastasis to bone. *Cancer Cell* 2003; 3 (6): 537–49. [PubMed: 12842083]
27. Minn AJ, Gupta GP, Siegel PM, et al. Genes that mediate breast cancer metastasis to lung. *Nature* 2005; 436 (7050): 518–24. [PubMed: 16049480]
28. Riethmuller G, Klein CA. Early cancer cell dissemination and late metastatic relapse: clinical reflections and biological approaches to the dormancy problem in patients. *Semin Cancer Biol* 2001; 11 (4): 307–11. [PubMed: 11513566]
29. Weigelt B, Wessels LF, Bosma AJ, et al. No common denominator for breast cancer lymph node metastasis. *Br J Cancer* 2005; 93 (8): 924–32. [PubMed: 16189523]
30. Weigelt B, Glas AM, Wessels LF, et al. Gene expression profiles of primary breast tumors maintained in distant metastases. *Proc Natl Acad Sci U S A* 2003; 100 (26): 15901–5. [PubMed: 14665696]
31. Radford DM, Phillips NJ, Fair KL, et al. Allelic loss and the progression of breast cancer. *Cancer Res* 1995; 55 (22): 5180–3. [PubMed: 7585569]
32. Steeg PS. Tumor metastasis: mechanistic insights and clinical challenges. *Nat Med* 2006; 12 (8): 895–904. [PubMed: 16892035]
33. Sekita N, Suzuki H, Ichikawa T, et al. Epigenetic regulation of the KAI1 metastasis suppressor gene in human prostate cancer cell lines. *Jpn J Cancer Res* 2001; 92 (9): 947–51. [PubMed: 11572762]
34. Xue C, Plieth D, Venkov C, et al. The gatekeeper effect of epithelial-mesenchymal transition regulates the frequency of breast cancer metastasis. *Cancer Res* 2003; 63 (12): 3386–94. [PubMed: 12810675]
35. Weigelt B, Peterse JL, van 't Veer LJ. Breast cancer metastasis: markers and models. *Nat Rev Cancer* 2005; 5 (8): 591–602. [PubMed: 16056258]
36. Phelan CM, Rebbeck TR, Weber BL, et al. Ovarian cancer risk in BRCA1 carriers is modified by the HRAS1 variable number of tandem repeat (VNTR) locus. *Nat Genet* 1996; 12 (3): 309–11. [PubMed: 8589723]
37. Jakubowska A, Gronwald J, Menkiszak J, et al. The RAD51 135 G>C polymorphism modifies breast cancer and ovarian cancer risk in Polish BRCA1 mutation carriers. *Cancer Epidemiol Biomarkers Prev* 2007; 16 (2): 270–5. [PubMed: 17301259]
38. Svenson KL, Von Smith R, Magnani PA, et al. Multiple trait measurements in 43 inbred mouse strains capture the phenotypic diversity characteristic of human populations. *J Appl Physiol* 2007; 102 (6): 2369–78. [PubMed: 17317875]
39. Frankel WN. Taking stock of complex trait genetics in mice. *Trends Genet* 1995; 11 (12): 471–7. [PubMed: 8533162]
40. Grubb SC, Churchill GA, Bogue MA. A collaborative database of inbred mouse strain characteristics. *Bioinformatics* 2004; 20 (16): 2857–9. [PubMed: 15130929]
41. Schadt EE, Monks SA, Drake TA, et al. Genetics of gene expression surveyed in maize, mouse and man. *Nature* 2003; 422 (6929): 297–302. [PubMed: 12646919]
42. Bystrykh L, Weersing E, Dontje B, et al. Uncovering regulatory pathways that affect hematopoietic stem cell function using 'genetical genomics'. *Nat Genet* 2005; 37 (3): 225–32. [PubMed: 15711547]
43. Chesler EJ, Lu L, Shou S, et al. Complex trait analysis of gene expression uncovers polygenic and pleiotropic networks that modulate nervous system function. *Nat Genet* 2005; 37 (3): 233–42. [PubMed: 15711545]
44. Shockley KR, Churchill GA. Gene expression analysis of mouse chromosome substitution strains. *Mamm Genome* 2006; 17 (6): 598–614. [PubMed: 16783641]
45. Minn AJ, Gupta GP, Padua D, et al. Lung metastasis genes couple breast tumor size and metastatic spread. *Proc Natl Acad Sci U S A* 2007; 104 (16): 6740–5. [PubMed: 17420468]
46. Le Voyer T, Lu Z, Babb J, et al. An epistatic interaction controls the latency of a transgene-induced mammary tumor. *Mamm Genome* 2000; 11 (10): 883–9. [PubMed: 11003704]
47. Lifsted T, Le Voyer T, Williams M, et al. Identification of inbred mouse strains harboring genetic modifiers of mammary tumor age of onset and metastatic progression. *Int J Cancer* 1998; 77 (4): 640–4. [PubMed: 9679770]

48. Le Voyer T, Rouse J, Lu Z, et al. Three loci modify growth of a transgene-induced mammary tumor: suppression of proliferation associated with decreased microvessel density. *Genomics* 2001; 74 (3): 253–61. [PubMed: 11414753]
49. Hunter KW, Broman KW, Voyer TL, et al. Predisposition to efficient mammary tumor metastatic progression is linked to the breast cancer metastasis suppressor gene Brms1. *Cancer Res* 2001; 61 (24): 8866–72. [PubMed: 11751410]
50. Park YG, Clifford R, Buetow KH, et al. Multiple cross and inbred strain haplotype mapping of complex-trait candidate genes. *Genome Res* 2003; 13 (1): 118–21. [PubMed: 12529314]
51. Park YG, Zhao X, Lesueur F, et al. Sipal is a candidate for underlying the metastasis efficiency modifier locus Mtes1. *Nat Genet* 2005; 37 (10): 1055–62. [PubMed: 16142231]
52. Crawford NP, Ziogas A, Peel DJ, et al. Germline polymorphisms in SIPA1 are associated with metastasis and other indicators of poor prognosis in breast cancer. *Breast Cancer Res* 2006; 8 (2): R16. [PubMed: 16563182]
53. Wang W, Wyckoff JB, Frohlich VC, et al. Single cell behavior in metastatic primary mammary tumors correlated with gene expression patterns revealed by molecular profiling. *Cancer Res* 2002; 62 (21): 6278–88. [PubMed: 12414658]
54. Montel V, Huang TY, Mose E, et al. Expression profiling of primary tumors and matched lymphatic and lung metastases in a xenogeneic breast cancer model. *Am J Pathol* 2005; 166 (5): 1565–79. [PubMed: 15855655]
55. Yang H, Crawford N, Lukes L, et al. Metastasis predictive signature profiles pre-exist in normal tissues. *Clin Exp Metastasis* 2005; 22 (7): 593–603. [PubMed: 16475030]

A. Progression Model

B. Transient Compartment Model

Figure 1.

Comparison of the two models of metastasis efficiency. A. Progression model. In the progression model a series of random mutational events occurs within a tumor resulting in a small subpopulation that acquires a full metastatic potential. B. Transient compartment model. In the transient model, all tumor cells have the ability to invade and metastasize, but due to reversible epigenetic events and position within the tumor, only few cells will maintain the ability at all times.

Figure 2. Factors affecting metastatic susceptibility. The probability that an individual will develop a metastasis disease is affected by combined factors; somatic mutation within the primary tumor, germline polymorphisms and environmental exposure. Therefore, studying the genetic background plays an essential role in determining whether a patient will be more predisposed to metastasis. Primary tumors derived from patients with a high metastatic genotype will display a pro-metastatic gene expression signature, which in part, is due to inherited polymorphisms.