BM-24MULTI-GENE METHYLATION ANALYSIS TO IDENTIFY SIGNATURE GENES FOR BRAIN METASTASIS FROM PRIMARY BREAST TUMORS

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Tumor metastasis to the brain is a common and deadly development in certain cancers; 18-30% of breast tumors metastasize to the brain. The contribution that gene silencing through epigenetic mechanisms plays in metastasis is not well understood. To identify epigenetic drivers of brain metastasis we have combined a candidate gene screen and Genome-wide methylation analysis of metastatic brain tumors that originated from primary breast tumors. From a screen of 85 candidates and an independent comparison of genome-wide methylation profiles in brain metastases we have identified genes that are frequently methylated in breast-to-brain metastases and infrequently methylated in primary breast tumors. We have identified gene methylation that either occurs early in tumour evolution (methylation is present in primary tumors that metastasize) or late in tumour evolution (methylation is only present in the brain metastasis). Many of the genes identified are involved in transcriptional control, either by DNA binding or through mRNA regulation (MicroRNAs etc.). We are carrying out in vitro assays to determine if epigenetic deregulation of these genes contributes to the metastatic phenotype: CCDC8 and GALNT9 are methylated in 87% and 53% of breast-to-brain metastases respectively, knock-down of these genes by RNAi resulted in a significant migratory (p = 0.0033, p = 0.0253) advantage of breast cancer cell lines. BNC1 and L3MBTL1 are methylated in 73% and 67% of breast-to-brain metastases respectively, knock-down by RNAi resulted in a significant migratory (p = 0.0302, p = 0.0061) and invasive (p = 0.0012, p = 0.0161) advantage to breast cancer cell lines. These early data suggest that this approach has the potential to identify genes deregulated in the process of tumour metastasis to the brain. Further analysis is required to determine if these genes may be used as therapeutic targets or prognostic markers.