Identification of predictive biomarkers for dasatinib treatment of metastatic melanoma.

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Background: Metastatic melanoma remains an almost certainly fatal disease. Current therapies fail to improve survival rates; therefore it is critical to identify alternate therapies for this disease. Dasatinib, a multi-target tyrosine kinase inhibitor, has anti-proliferative and anti-invasive effects *in vitro* in melanoma. However, clinical trials with dasatinib have demonstrated modest activity in metastatic melanoma. Identification of predictive biomarkers for dasatinib may facilitate selection of melanoma patients that are more likely to respond to dasatinib. **Methods:** We examined the effect of dasatinib on proliferation in 8 melanoma cell lines. We analyzed the expression of a previously identified 6-gene panel (ANXA1, CAV-1 CAV-2, EphA2, IGFBP2 and PTRF) of biomarkers in the panel of cell lines. We correlated response to dasatinib with expression of each gene at both the mRNA and protein level. ANXA1, CAV-1 and EphA2 expression were analyzed in 121 melanoma tumor samples by immunohistochemical (IHC) staining. ***Results:*** Dasatinib inhibits growth in 3 of the 8 melanoma cell lines tested. mRNA expression of the 6-gene markers did not correlate with response whilst higher protein expression of ANXA1 ($p=0.04$), CAV-1 ($p=0.05$) and EphA2 ($p=0.02$) correlated significantly with response to dasatinib in the panel of cell lines. Furthermore, the 3 dasatinib sensitive cell lines expressed high levels of all three markers. Although ANXA1 was detected in all of the resistant cell lines, CAV1 and EphA2 were

only detected in 3 of the 5, and none of the resistant cell lines expressed high levels of all three markers. ANXA1 protein was detected in 82 % (97/119) of tumors, CAV-1 in 45 % (54/121) and EphA2 in 75 % (90/120). 34 % (38/112) of the melanoma specimens expressed all three markers and 12 % (13/112) demonstrated high levels of ANXA1, CAV-1 and EphA2 staining (2+ (moderate) or 3+ (strong) by IHC). ***Conclusions:*** High levels of ANXA1, CAV-1 and EphA2 correlate with response to dasatinib in melanoma cell lines. Immunohistochemical analysis suggests that 12% of melanomas (13/112) showed high levels of staining for the three markers. This subgroup may represent a population of patients who may derive clinical benefit from dasatinib treatment.
