Title: Imatinib and Nilotinib increase glioblastoma cell invasion via Abl-independent stimulation of p130Cas / RAP1A and FAK signaling

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Abstract: Imatinib was the first targeted tyrosine kinase inhibitor to be approved for clinical use, and is first-line therapy for Philadelphia chromosome (Ph+)-positive chronic myelogenous leukaemia. We show that treatment of human glioblastoma multiforme (GBM) tumour cells with imatinib and the closely-related drug, nilotinib, strikingly increases tyrosine phosphorylation of p130Cas, focal adhesion kinase (FAK) and the downstream adaptor protein Paxillin (PXN), resulting in enhanced cell migration and invasion. Imatinib and nilotinib-induced tyrosine phosphorylation was dependent on expression of p130Cas and FAK activity and was independent of known imatinib targets including Abl, platelet derived growth factor receptor beta (PDGFRβ) and the collagen receptor DDR1. Pharmacological inhibition of the serine threonine phosphatase, PP2A, resulted in increased p130Cas tyrosine phosphorylation, whilst activation of PP2A inhibited the imatinib & nilotinib stimulated increase. Imatinib and nilotinib treatment increased RAP1A-GTP levels and increased two dimensional cell migration and three dimensional radial spheroid invasion in collagen. In addition, silencing of p130Cas, RAP1A, inhibition of FAK activity, or activation of PP2A all strongly reduced imatinib & nilotinib stimulated invasion. Importantly, imatinib & nilotinib increased tyrosine phosphorylation of p130Cas, FAK, PXN and radial spheroid invasion in stem cell lines isolated from human glioma biopsies. These findings identify a novel mechanism of action in GBM cells for two well established front line therapies for cancer resulting in enhanced tumour cell motility.

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