DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF CONSTITUTIVE AND INDUCED pSTAT3, pSTAT5, pAKT and pERK in PLASMA CELL DISORDERS BY PHOSPHO FLOW.

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Identification of aberrant expression in signal transduction pathways is becoming increasingly relevant to the diagnosis, prognosis and pharma co-dynamics of haematological malignancies.

Our aim was to demonstrate the diagnostic and prognostic relevance of constitutive and IL-6 induced pSTAT3, pSTAT5, pAKT and pERK in patients with plasma cell disorders including multiple myeloma (MM), monoclonal gammopathy of uncertain significance (MGUS) and plasma cell leukaemia (PCL) and to further our knowledge of the acquired dysfunction in these signaling pathways. 65 frozen bone marrow samples collected from MM patients at diagnosis (2000-2010) and 10 age-matched controls were stained with anti CD 38, 138, 45 and 130 (IL-6 receptor). Constitutive and IL-6 induced levels of pSTAT3, pSTAT5, pERK and pAKT were measured using phospho-flow. MGUS (n=9) and PCL (n=6) samples were also analysed. CD19 and CD56 staining was used to separate CD38++ malignant from non-malignant plasma cells. Constitutive expression of pSTAT3, pSTAT5, pAKT, pERK or IL-6 receptor did not differentiate between plasma cell disorders nor have any prognostic significance. MM patients with up regulated levels of pSTAT3 following activation with IL-6 had a better overall survival, 55 versus 23 months, ($\chi 2$=13.6, P<0.0003). In a multivariate analysis with ISS, IL-6 induced pSTAT3 retained prognostic significance (p<0.001). IL-6 induced signaling was associated with CD45 expression. This is the first comprehensive phospho flow study of constitutive and cytokine-induced signaling proteins in patients with monoclonal gammopathies. Constitutive levels of these phosphorylated proteins do not assist the differential diagnosis of plasma cell disorders but could be used to identify patients suitable for targeted inhibitor therapy. IL-6 induced pSTAT3 is an independent predictor of overall survival.