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Molecularbiological studies on human myeloma cell lines: The role of ABL tyrosine kinase in myeloma

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Recently, two major technological developments have opened new pathways in MM research, the microarray technology and a method to obtain a pure population of normal plasmablasts. The difference in expression of genes between normal and tumor plasma cells reveals new genes that could be important in MM tumorigenesis and therefore interesting new therapeutic targets. One of the genes overexpressed in MM is abl, which encodes a tyrosine kinase, responsible for differentiation of the cell, cell division, cell adhesion and stress response.
Semiquantitative RT-PCR showed that abl is overexpressed about twofold in MM cell lines compared to PPCs, but there is no ABL protein increase of note detectable in the MM cell samples by the western blot assay.
Looking at ABL autophosphorylation using immunoprecipitation techniques, we were able to demonstrate that this kinase is activated continuously in some myeloma cell lines and can be activated by IL-6, a central cytokine in MM tumorigenesis.
Blocking the ABL tyrosine kinase with the specific small molecule inhibitor STI 571, recently developed for CML treatment, an about 10fold lower sensitivity was found in the MM cell lines as compared to the CML cell line K562.
When the essential MM cytokine IL-6 is absorbed or reduced in quantity with an anti-IL-6 mAb B-E8 (in concentrations already tested in clinical studies), and thus the IL-6 signal becomes a

limiting factor, the effect of the ABL inhibitor STI 571 in MM increases significantly (combination with significantly higher growth inhibition than STI 571 alone, P=0.005) and the dose needed to inhibit 50% of the cell proliferation becomes applicable to the human body with only low side effects. We evaluated 0.03 µg/ml B-E8 combined to 3µM of STI 571 as an effective dose leading to 64% growth inhibition (compared to 36% for STI 571 3µM alone and 26% for B-E8 0.03µg/ml alone).

This led us to believe that ABL could be a potential therapeutic target in MM treatment, especially if also based on a better understanding of MM molecular basics.