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Editorial
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# The AP-1 Family Member JunB: A Novel Potential Target for Therapy in Multiple Myeloma

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## Editorial

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by clonal expansion of plasma cell within the bone marrow (BM), and is often preceded by a premalignant condition named gammopathy of undetermined significance (MGUS), defined by the presence of serum monoclonal protein <30 g/L, clonal BM plasma cells <10%, in the absence of renal failure, anemia, bone lesions, hypercalcemia, or amyloidosis [1]. MGUS cases may progress to MM in about 0.5% to 1% per year [1]. An intermediate stage between MGUS and MM exists, and it is known as smoldering MM (S-MM): it is characterized by the presence of serum monoclonal component ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal bone marrow plasma cells 10% to 60%. Moreover, patients do not present with myeloma defining events or amyloidosis. S-MM may progress to MM in about 10% per year, in the first five years after diagnosis [1]. MM is defined by ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma, evidence of end organ damage including hypercalcaemia, renal insufficiency, anaemia, bone lesions [1]. More recently, the International Myeloma Working Group consensus has defined as MM, also those cases where patients present with one or more features including clonal BM plasma cell ≥ 60%, involved/uninvolved serum free light chain ratio ≥ 100, >1 focal lesions on MRI studies [1].

Despite several advances in the field of MM research, MM remains an incurable condition and therefore there is a need for identifying novel potential therapeutic targets.

Fan et al. [2], from K. Podar's Group, recently described, for the first time, how JunB, a member of the transcription factor activator/activating protein-1 (AP-1) family, is involved in MM pathogenesis; and defined JunB as a promising novel therapeutic target in MM.

Specific AP-1 family members can act as either oncogenes or tumor suppressors, depending on tumor cell type, tumor genetic background, stage, differentiation grading and, importantly, tumor milieu [3-7]. For instance, the AP-1 family member JunB is a close homologue of the transcription factor c-Jun with tumour-suppressive function in solid tumors [8]. Nevertheless, its role in multiple myeloma was not known and it has been just reported by Fan et al. [2].

In this study, Authors described JunB as responsible for enhancing MM cell proliferation, survival, as well as drug resistance. Collectively, Fan et al. [2] findings highlight the relevance of JunB not only as a novel contributor to MM pathogenesis, but also provide the preclinical rationale for targeting JunB as novel therapeutical intervention in MM.

Authors have first documented how MM cell lines and BM patients' derived plasma cells present with a significant and rapid induction of JunB when co-cultured with primary BM stromal cells, thus further corroborating the relevance of the BM milieu in supporting MM pathogenesis [2]. Indeed, the functional relevance of the BM milieu in supporting pathogenesis of several hematologic malignancies, including both lymphoid and myeloid neoplasms, has been widely accepted [9-21].

Of note, bioinformatics analysis also showed a significant increase of JunB going from normal plasma cells, to MGUS, smoldering MM (sMM)-, and MM-derived plasma cells. This led Authors to hypothesize that JunB may indeed crucially partecipate to MM development and pathogenesis. Subsequent studies were performed using JunB-silenced MM cells, demonstrating that JunB-ablation was responsible for inhibition of MM cell proliferation and was able to reduce MM tumor growth *in vivo* [2].

Mechanistically, Authors also provided novel insights into the molecular basis explaining JunB role in MM cell growth. Specifically, JunB-silenced cells presented with a significant enrichment

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for apoptotic-related pathways, after IL-6 stimulation. Some of the most affected genes were Caspase-3, -8, -FADD, BID, DFFB, APAF1 and BIRC3; while JunB-knockdown led to inhibition of several pro-survival-related pathways, including PI3K, NF-kB, JAK/STAT and MAPK [2].

Authors were also able to demonstrate a role of JunB in mediating drug resistance, a phenomenon that ultimately leads to MM disease relapses: specifically, by engineering MM cells to stably express an inducible JunB fusion protein, with the hormone-binding domain of the human estrogen receptor, JunB was shown to mediate drug resistance to both steroids and proteasome inhibition [2].

Finally, the prognostic relevance of JunB within the clinical setting was also evaluated with the demonstration that JunB levels were significantly higher at the baseline than at time of MM relapse. These observations led Authors to hypothesize that MM cells with high JunB are dependent from the microenvironment; and that once they become more aggressive and therefore less dependent or totally independent form the BM milieu, MM cells do not longer depend or rely on JunB [2]. This observation has important clinical implications for the design of future clinical trials with JunB targeting agents.

In summary, Fan et al. [2] have clarified, for the first time, the mechanism by which JunB acts as a crucial regulator of MM pathogenesis and an inducer of drug resistance. All together, these very interesting results provide the preclinical rationale for testing JunB-neutralizers as a novel treatment for MM patients.

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