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## Myeloma Cell Self-Renewal Depends on JAG2 Expression and Is Mediated by IGF1 or SCF Loop

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### Abstract

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The purpose of this study was to identify the pathways associated with the ability of human myeloma cells (HMCLs) to spontaneous self-renew in a serum-free semi-solid human collagen-based assay. Among 32 HMCLs analyzed, 8 were able to grow spontaneously (from 5% to 35% of seeded cells) without any addition of cytokines or growth factors and this capacity to grow correlated with the presence of *RAS* mutations ( $p=0.04$ ). Gene expression profile analysis of HMCLs identified one gene, *JAG2*, overexpressed in HMCLs that are able to self-renew. Interestingly, flow cytometry analysis of *JAG2* expression showed that the level of membrane *JAG2* expression positively correlated ( $r=0.87$ ) to the percentage of colony formation ( $p=0.004$ ). Blocking Jag-Notch interactions with Notch-Fc chimeric molecules impaired self-colony formation underlying a role for Jag-Notch pathway in colony formation. Furthermore, direct *JAG2* silencing in two independent HMCLs (KMM1 and JJN3) prevented colony formation. Moreover, xenografts in SCID mice showed that *JAG2* silencing fully impaired tumor growth of both KMM1 and JJN3. RT-PCR evaluation of *JAG2* expression showed that 20 of 30 CD138+ purified primary myeloma cells expressed *JAG2* and a Jag2+ subpopulation was identified by flow cytometry within primary CD138+ MM cells of patients at diagnosis or relapse.



We further identified the growth factors involved in the self-renewal. By using blocking anti-IGF1R Ab or C-KIT inhibitor (imatinib mesylate), we showed that self-renewal of HMCLs was dependent on IGF1/IGF1R (5 of 8) or on C-KIT/SCF (1) or on both loops (2 of 8). Of note, C-KIT<sup>+</sup> HMCLs expressed high JAG2 level at the cell membrane that was decreased by imatinib mesylate. Interestingly, none HMCL self-renewal was dependent on IL6/IL6R loop despite the high efficiency of paracrine IL6 to induce colony formation in most HMCLs. To address expression of C-KIT/SCF and IGF1R/IGF1 in primary myeloma cells, we used public data from patients at diagnosis published by Arkansas University. Expression of C-KIT and IGF1R was found in 56% and 50% of patients at diagnosis, respectively: 53% of patients express one or the other receptor, 27% express both and 20% express none. Expression of receptors is not similar with regard to the molecular classification of patients as previously shown by cytometry: indeed, MS patients underexpress C-KIT ( $p < 0.001$ ) but overexpress IGF1R ( $p < 0.001$ ), in full contrast to HY patients who overexpress C-KIT ( $p < 0.001$ ) but underexpress IGF1R ( $p < 0.001$ ). Moreover, IGF1R expression is lower on C-KIT<sup>+</sup> patients as compared with C-KIT<sup>-</sup> ones ( $p = 0.049$ ). Of note, CD-1 and CD-2 patients underexpress both C-KIT ( $p = 0.039$ ) and IGF1R ( $p < 0.001$ ). IGF1 and SCF are produced by the microenvironment although IGF1 (but not SCF) mRNA was found in myeloma cells too. Altogether, these data suggest that IGF1 and SCF could be the main growth factors for 80% of the patients. Blocking these two tyrosine kinase receptors (in good agreement with their expression in patients) as well as Jag2/Notch interactions could decrease myeloma progression and/or relapse and thus increase survival.

## Disclosures:

No relevant conflicts of interest to declare.

**Topics:** insulin-like growth factor i, myeloma cells, proto-oncogene protein c-kit, insulin-like-growth factor i receptor, growth factor, flow cytometry, imatinib mesylate, interleukin-6, cytokine, gene expression profiling

## Author notes

\*Asterisk with author names denotes non-ASH members.

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Francesca Morandi et al., Blood, 2006

Immune control of hair growth

Lisa D. Chong, Science, 2017

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