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

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MYELOMA - BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY I | NOVEMBER 19, 2010

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

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Blood (2010) 116 (21): 127.

https://doi.org/10.1182/blood.V116.21.127.127

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+ 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*$^{+}$ patients as compared with *C-KIT*$^{-}$ 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.

Volume 116, Issue 21

November 19 2010

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Paola Storti et al., Blood, 2011

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Paola Storti et al., Blood, 2014

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Immune control of hair growth
Lisa D. Chong, Science, 2017

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