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Correspondence

To the editor:

Components of the revised International Prognostic Scoring System and outcome after hematopoietic cell transplantation for myelodysplastic syndrome

Despite the proven curative potential of allogeneic hematopoietic cell transplantation (HCT) for patients with myelodysplastic syndrome, posttransplant relapse is common in patients with high-risk cytogenetics. One strategy to improve post-HCT outcome may be to accurately identify high-risk patients in order to intervene with novel therapies aimed at reducing relapse after transplantation. Many disease factors have been independently associated with increased risk of relapse and mortality after transplant, three of which—marrow myeloblast count, cytogenetics, and peripheral blood cytopenias—are components of the International Prognostic Scoring System (IPSS).[1] Although it was developed in the nontransplant setting, the IPSS has been useful for estimating posttransplant prognosis as well.[2,3] The recent revision of the IPSS (IPSS-R)[4] places greater weight on cytogenetic risk within the prognostic model after incorporating a more refined system of classifying cytogenetic abnormalities.[5] In an analysis of more than 1000 patients, we showed that this new cytogenetic classification system enhances prognostic accuracy for transplanted patients over the previous system, primarily by distinguishing between patients with poor and very poor-risk cytogenetics.[6] With the subsequent reporting of the IPSS-R, we evaluated the other components of the final IPSS-R model to determine whether those parameters added to the prognostic power of cytogenetics in predicting post-HCT outcome.

We reviewed results in 544 patients with complete IPSS-R data who underwent HCT between 1996 and 2010, all of whom were included in the previous publication.[6] As with the initial analysis, increased cytogenetic risk was associated with increased relapse, nonrelapse mortality, and overall mortality after HCT (Table 1). Adjustment for blast count, hemoglobin level, platelet count, and neutrophil count did not qualitatively change the association of cytogenetic risk and outcome. Similarly, lactate dehydrogenase (LDH),[4,7] also included in the IPSS-R report, albeit not reflected in the IPSS-R scoring system, did not significantly alter the impact of cytogenetics by themselves.

Thus, our analysis of the impact of the individual components of the IPSS-R and LDH on post-HCT outcome confirms the central role of cytogenetics. The additional risk factors included in the IPSS-R, as well as LDH, did not appear to add significantly to post-HCT prognosis. Those factors appear to play a lesser role in the transplant setting than in nontransplanted patients, presumably because parameters such as anemia, neutropenia, and thrombocytopenia are corrected by HCT and do not necessarily imply that the myelodysplastic syndrome clonal precursors have been eradicated. A criticism of the current IPSS-R cytogenetic classification system is that it does not include recently identified molecular markers such as *TP53*, *ASXL1*, and *SF3B1*,[8,9] which do have clear prognostic implications. Because these markers are being incorporated into prognostic models, it is likely that the weight of traditional markers, such as morphologic myeloblast count, cytopenias, and inflammatory markers, will diminish.

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Table 1. Univariate and multivariable models for posttransplant outcome

		Relapse			Overall mortality			Nonrelapse mortality			Treatment failure*		
Cytogenetic risk[5]	No. of patients†	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Univariate model													
Good	270	1			1			1			1		
Intermediate	108	0.98	0.62-1.57	.94	1.11	0.82-1.50	.50	1.21	0.83-1.76	.33	1.11	0.83-1.49	.49
Poor	73	1.54	0.98-2.43	.06	0.98	0.68-1.41	.92	0.75	0.45-1.26	.28	1.09	0.78-1.53	.62
Very poor	82	5.07	3.40-7.56	<.0001	3.35	2.51-4.46	<.0001	2.95	1.97-4.41	<.0001	3.83	2.89-5.08	<.0001
Multivariable model adjusting for blast count, hemoglobin, platelet count, neutrophil count, and LDH													
Good	270	1			1			1			1		
Intermediate	108	0.94	0.58-1.51	.80	1.02	0.75-1.39	.89	1.08	0.74-1.59	.68	1.03	0.77-1.39	.83
Poor	73	1.59	1.00-2.52	.05	0.95	0.66-1.37	.80	0.70	0.42-1.19	.19	1.07	0.76-1.51	.69
Very poor	82	5.19	3.42-7.87	<.0001	3.05	2.26-4.11	<.0001	2.54	1.66-3.88	<.0001	3.59	2.67-4.83	<.0001

HR, hazard ratio.
*Death or relapse.
†Patients with very good cytogenetics are not included due to small numbers (n = 9); 2 patients with unknown cytogenetics.

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To the editor:

TCF-1 mediates repression of Notch pathway in T lineage–committed early thymocytes

Notch-derived signals are essential for specification of hematopoietic progenitors to T-cell lineage and for promotion of β-selection at the CD4⁻CD8⁻ double-negative 3 (DN3) stage. However, these signals are not required for further thymocyte maturation.[1] Accordingly, the expression of *Notch1* and its target genes, including *Ptcra* (encoding pre–T-cell receptor alpha [TCRα]), markedly decreases in late DN3 and DN4 cells.[2,3] *Notch1* downregulation has been attributed to pre-TCR–induced Id3, which antagonizes the

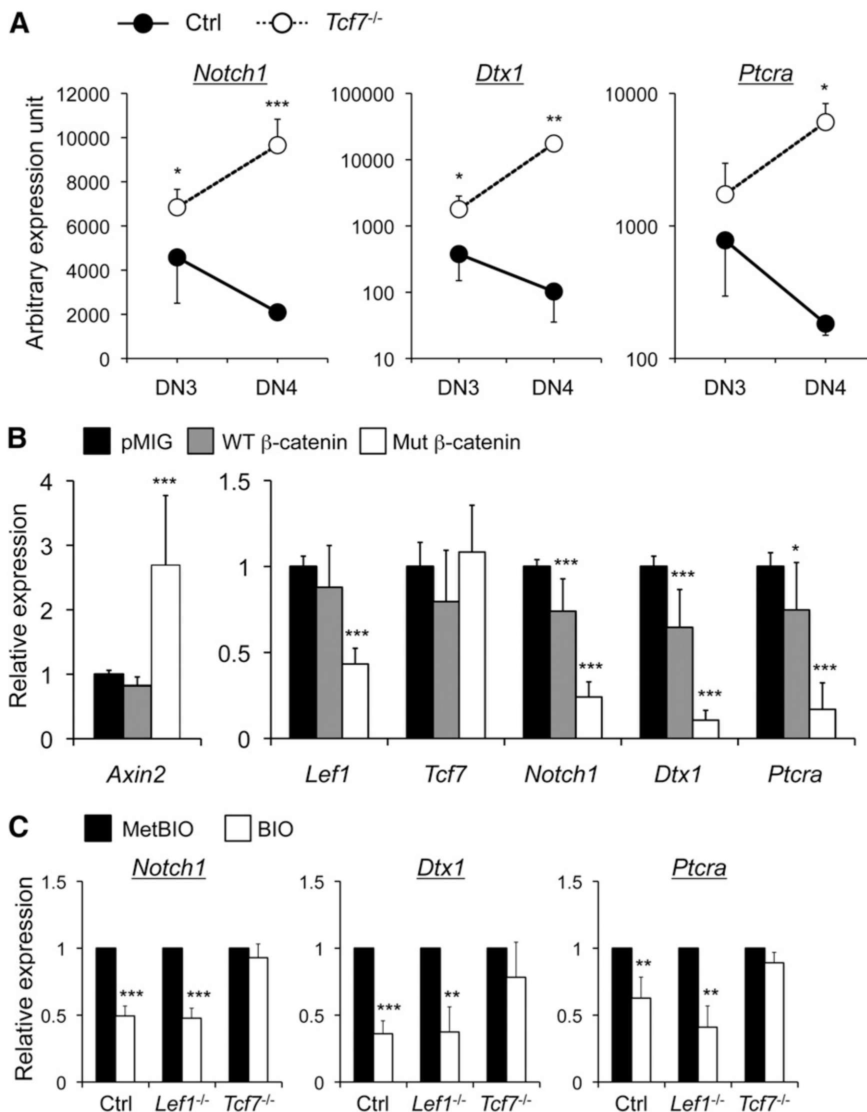

Figure 1. TCF-1 and activated β-catenin negatively regulate *Notch1* and its target genes in DN3 thymocytes. (A) Elevated expression of *Notch1* and its target genes in TCF-1–deficient DN3 and DN4 thymocytes. *Tcf7*$^{-/-}$ mice were age 8 weeks or younger and without overt signs of thymic malignancy at the time of analysis. DN subsets were sorted from lineage-negative thymocytes from *Tcf7*$^{-/-}$ mice or littermate controls and assessed for gene expression. The relative expression level of individual genes was obtained by normalizing to the *Hprt1* housekeeping gene. Data are means ± standard deviation from 1 of 3 experiments with similar results (n ≥ 3 in each experiment). (B) Activated β-catenin represses the expression of *Notch1* and its targets in DN3 thymocytes. Lineage-negative DN thymocytes were cultured on OP9-DL1 stromal cells[10] overnight in the presence of interleukin-7 (5 ng/mL) and then infected with empty retroviral vector pMIG or that expressing wild-type (WT) or mutant β-catenin. The mutant β-catenin has internal deletions of its *N*-terminal Ser/Thr phosphorylation sites and is therefore constitutively active.[8] Twenty-four hours later, the GFP⁺ DN3 thymocytes were sorted and analyzed for expression of indicated genes. After normalization to *Hprt1*, the expression of each gene in pMIG-infected cells was arbitrarily set to 1, and its relative expression in the presence of WT or mutant β-catenin was then calculated. Data were pooled from at least 3 independent experiments (n ≥ 7). Similar data were obtained with DN4 cells (not shown). (C) β-catenin–mediated Notch repression depends on TCF-1. DN3 thymocytes were sorted from control mice, Vav1-Cre *Lef1*$^{-/-}$ [6] or *Tcf7*$^{-/-}$, cultured in the presence of 5 μM MetBIO or BIO for 6 hours, and then harvested for gene expression analysis. After normalizing to *Hprt1*, the expression of each gene in MetBIO-treated cells was arbitrarily set to 1, and its relative expression in BIO-treated samples was then calculated. Data are pooled from 2 independent experiments (n ≥ 3). *, $P < .05$; **, $P < .01$; ***, $P < .001$ by Student *t* test. Note that although multiple TCF/LEF binding motifs were found within "–30 kb ~ +10 kb" of transcription initiation sites of the *Notch1*, *Dtx1*, and *Ptcra* genes, we did not find enriched binding of TCF-1 to these motifs in DN3 thymocytes. Further studies are necessary to determine if repression of *Notch1* and its targets by TCF-1 is mediated by direct regulation *via* more distal TCF/LEF motifs or by indirect mechanisms.

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