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Title: Higher Sclerostin/*SOST* expression is associated with lower percentage of circulatory blasts and better prognosis in patients with myelofibrosis

Authors: Marko Lucijanic[1], Ana Livun[2], Katarina Marija Tupek[2], Tajana Stoos-Veic[3,4], Vlatko Pejsa[1,5], Rajko Kusec[1,2,5]

Affiliations:

[1] Hematology Department, University Hospital Dubrava, Zagreb, Croatia

[2] Division of Molecular Diagnosis and Genetics, Clinical Department of Laboratory Diagnostics, University Hospital Dubrava, Zagreb, Croatia

[3] Department of Clinical Cytology and Cytometry, University Hospital Dubrava, Zagreb, Croatia

[4] University of Osijek, Faculty of Medicine, Osijek, Croatia

[5] University of Zagreb, School of Medicine, Zagreb, Croatia

Corresponding author: Marko Lucijanic, MD PhD, Hematology Department, University Hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb. Email: markolucijanic@yahoo.com

ORCID: http://orcid.org/0000-0002-1372-2040

Dear Editor,

Sclerostin (a product of *SOST* gene) acts as a main negative regulator of bone metabolism, exerting its properties through inhibition of canonical-WNT signaling-pathway (cWNT) in osteoblasts [1]. It is produced by osteocytes and bone marrow (BM) cells. cWNT activation is implicated in pathogenesis of Philadelphia chromosome negative myeloproliferative neoplasms (Ph- MPNs) [2,3], diseases characterized by remodelling of BM stroma and development of BM fibrosis/osteosclerosis during course of the disease. We aimed to investigate Sclerostin/*SOST* expression in BM tissues of patients with primary (PMF) and secondary post Ph- MPN myelofibrosis (SMF) and to assess its clinical correlations.

We retrospectively investigated Sclerostin/*SOST* expression in BM of 66 diseased patients (51 PMF, 15 post-PV/post-ET-SMF, diagnoses were established according to the WHO [4] and the IWG-MRT [5] criteria) and 18 age- and sex-matched controls (limited-stage aggressive Non-Hodgkin-lymphoma patients without BM involvement) using immunohistochemistry (IHC; Sclerostin 21933-1-AP rabbit polyclonal Proteintech primary antibody) and real-time polymerase-chain-reaction (RT-PCR; SOST Hs00228830_m1 Thermo Fischer Scientific TaqMan assay; evaluated from BM aspirates). Sclerostin expression was expressed as a percentage of positive cells. *SOST* mRNA expression was normalized to *Abl* and expressed as a ΔCT value. Correlations with clinical parameters were made. Optimal cut-off values for survival were determined using the ROC-curve-analysis. The Mann-Whitney-U-test, the Spearman-rank-correlation, the Cox-Mantel-log-rank-test [6] and the Cox-regression-analysis were used. Analyses were done using MedCalc-Statistical-Software ver.18 (MedCalc Software bvba, Ostend, Belgium). *P* values <0.05 were considered statistically significant. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All patients provided written informed consent.

Median age of patients was 67 years, 59% were males, 67% had grade II-III BM fibrosis, 70%, 11% and 2% were *JAK2*, *CALR* and *MPL* mutated, respectively. Median follow up of our cohort was 74

months with median overall survival of 69 months. Sclerostin/*SOST* expression did not significantly differ between PMF and SMF, nor between patients and controls. However, non-significantly higher expression was observed in myelofibrosis patients (both PMF and SMF) than in controls, result was near statistical significance for *SOST* (P=0.056). In diseased patients, higher Sclerostin expression measured by IHC was significantly correlated with lower percentage of circulatory blasts (Rho -0.28, P=0.042) and transfusion dependency (P=0.049). Higher *SOST* expression measured by RT-PCR was similarly significantly correlated with lower percentage of circulatory blasts (Rho -0.44, P=0.042), but also higher platelets (Rho 0.4, P=0.031) and smaller spleen size (Rho -0.6, P=0.001). We found no significant association of Sclerostin/*SOST* expression with *JAK2*, *CALR* and *MPL* mutation status or degree of bone marrow fibrosis. Patients with higher Sclerostin expression (HR=0.35, P=0.006) and higher *SOST* expression (HR=0.44, P=0.044) had superior overall survival than patients presenting with lower Sclerostin/*SOST* expression as shown in a Figure. This association remained significant for *SOST* (HR=0.21, P=0.025) after adjusting for age, gender and circulatory blasts (HR=1.06, P=0.002).

Several interesting observations emerge from our study. First, Sclerostin expression might affect stem-cell-mobilization. *SOST* deficient mice were shown to have reduced expression of CXCL12 [7] which is important for this process, and reverse situation with higher Sclerostin/*SOST* expression might be possible. Additionally, patients with higher Sclerostin/*SOST* expression experienced improved survival, effect which might be prognostically independent of reduction in circulatory blasts (known prognostic parameter in myelofibrosis [8]) and which is probably mediated through cWNT inhibition. Due to the limited number of patients, our study was probably underpowered to detect statistical significance of some existing clinical correlations. Nevertheless, our findings emphasize the role of bone metabolism regulating cytokines, such as Sclerostin, in pathogenesis of Ph- MPNs and suggest that cWNT inhibition might be an interesting therapeutic approach in myelofibrosis patients.

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Informed consent: All subjects provided written informed consent.

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Figure: A) Myelofibrosis patients presenting with higher Sclerostin (measured by immunohistochemistry) and B) *SOST* expression (measured by real-time polymerase chain reaction) experienced improved survival. The log-rank test was used.