XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari



Myeloproliferative disorders

# A NOVEL INSIGHT INTO THE ROLE OF CCM GENES IN MYELOPROLIFERATIVE NEOPLASMS

**C. Panuzzo, A. Bagherzadehsa, A. Ferrando, S. Rocco, A. Danzero, R. Vacca, B. Pergolizzi, C. Fava, F. Retta, D. Cilloni.**

*Università degli Studi di Torino, Dipartimento di Scienze Cliniche e Biologiche, Italy*

**Introduction:** Myeloid neoplasms (MNs) are clonal hematologic disorders characterized by chronic inflammation, oxidative stress, and increased risk of fibrotic and cardiovascular complications. Recent studies suggest that vascular and fibrotic pathways may contribute to disease progression. Among these, Cerebral Cavernous Malformation (CCM) genes, including KRIT1 (CCM1), CCM2, and PDCD10 (CCM3), regulate endothelial stability, oxidative homeostasis, and extracellular matrix organization and vesicle-mediated extracellular matrix dynamics. Here, we investigated CCM genes expression and function in leukemic and myeloproliferative models, focusing on mechanisms relevant to myelofibrosis.

**Methods:** Expression of KRIT1, CCM2, and CCM3 was analyzed in leukemic cell lines representing different myeloid lineages and in patient-derived samples. K562 cells were induced to differentiate toward the megakaryoblastic lineage using PMA treatment for 48 hours, a model approach to recapitulate key features of the megakaryocytic cells involved in myeloproliferative disease. Changes in CCM gene expression, lineage markers, and fibrosis-related genes were assessed by qPCR and Western blot. The role of CCM3 was further explored through gene silencing experiments to evaluate its impact on differentiation and fibrotic signaling.

**Results:**

Across leukemic models and patient samples, in particular myelofibrosis subjects, we consistently observed reduced KRIT1 and elevated CCM2 and CCM3 expression, correlating with pro-inflammatory and fibrotic profiles. During PMA-induced megakaryoblastic differentiation, lineage-specific markers confirmed successful differentiation, accompanied by a further decrease in KRIT1 and a marked increase in CCM2 and CCM3, as well as in key genes associated with inflammation, oxidative stress and fibrosis, supporting a role for CCM genes in megakaryocytic maturation. Importantly, CCM3 silencing impaired differentiation capacity and led to a downregulation of THBS1 and CXCR4, two genes strongly upregulated during normal differentiation and associated with extracellular matrix interaction and cellular adhesion. These findings indicate that CCM3 supports both the differentiation process and the acquisition of a pro-fibrotic megakaryocytic phenotype.

**Conclusions:** Our data reveal a distinctive CCM gene signature in myeloid models, characterized by low KRIT1 and high CCM3, linked to oxidative stress, inflammation, and fibrosis. Functional experiments demonstrate that CCM3 is required for proper megakaryocytic differentiation and for maintaining expression of extracellular and adhesion-related genes. Overall, these results suggest that CCM gene dysregulation may contribute to the aberrant differentiation and fibrotic remodeling observed in myeloproliferative neoplasms, offering potential new targets for therapeutic intervention.