

# The Long Arm (5q) Reaches Out to Erythroid Cells for a Knock-Out Punch!

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**D**ecrease in gene expression can wreak havoc on a cell. This turns out to be the case in 5q- syndrome subset of myelodysplastic syndromes (MDS). In yesterday's Plenary Session, Dr. Benjamin Ebert presented the results of a screen in which 40 genes that comprise the commonly deleted region (CDR) of 5q- were individually shut down. The inhibition of only one gene resulted in the death of erythroid cells while sparing megakaryocytes. These *in vitro* observations parallel the clinical features of 5q- syndrome, in which patients present with anemia and normal to high platelets. The pathology and clinical features of this disease are quite distinct from the other MDS subgroups. The patients are predominately female and present with macrocytic anemia and hypolobated megakaryocytes but have relatively normal myeloid cell counts. Disease progression is slow and fewer patients develop AML. Importantly, no point mutations or cryptic deletions have been found in the CDR genes of the remaining allele. The gene that was found to recapitulate the 5q- phenotype is RPS14, which encodes a structural protein of the 40S ribosomal subunit. Ribosome biosynthesis was found to be defective in samples from patients with 5q- syndrome but not in other MDS samples. Most importantly, the investigators show that over-expression of RPS14 restores normal differentiation of 5q- MDS CD34+ cells along the erythroid lineage. At least 50 percent reduction in the expression of RPS14 thus appears to be required for 5q- syndrome, although it may not be sufficient to explain the clonal dominance of MDS.

Mutation (or as here, a deletion) of a ribosomal structural protein gene as a causative event of a hematologic disease is not unique to 5q- syndrome. Several bone marrow failure diseases have now been linked to mutations of a ribosomal gene. Both RPS19 and RPS24 have been implicated in the congenital disease Diamond-Blackfan anemia. Defects in genes critical for ribosome biogenesis have been linked with Schwachman-Diamond syndrome, cartilage-hair hypoplasia, and dyskeratosis congenita. For 5q- syndrome specifically, rapidly proliferating erythroid precursors require high levels of ribosome biosynthesis. For 20 years, investigators have been searching for a tumor suppressor gene on the long arm of 5q as the causative event of 5q- MDS, but Dr. Ebert uncovered a completely unsuspected culprit by using the recently discovered RNAi technology to silence one gene at a time.