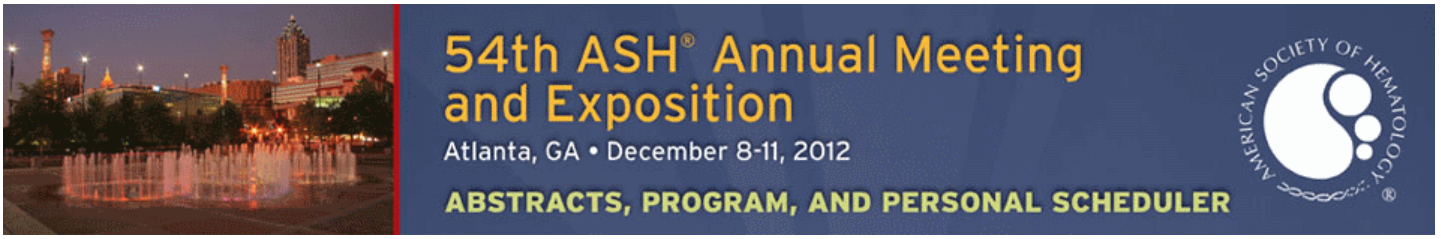


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# 3191 Resveratrol Induces Erythroid Maturation by Activating FOXO3 and Improves in Vivo Erythropoiesis in Normal and Beta -Thalassemic Mice

**Program:** Oral and Poster Abstracts
**Session:** 101. Red Cells and Erythropoiesis, Structure and Function, Metabolism and Survival, Excluding Iron: Poster III

**Monday, December 10, 2012, 6:00 PM-8:00 PM**
Hall B1-B2, Level 1, Building B (Georgia World Congress Center)

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Resveratrol is a polyphenolic stilbene with anti-oxidant, anti-inflammatory and anti-tumoral bioactivities . High concentrations of resveratrol (50 µM) have been reported to induce HbF synthesis in an in vitro model of normal and beta-thalassemic erythropoiesis (Fibach E. Int J Mol Med 2012; Rodrigue CM. BJH 2001) and to improve erythropoiesis in a mouse model for Fanconi Anemia (Zhang Q. Blood 2010). Beta thalassemia (b-thal) is characterized by ineffective erythropoiesis and increased cellular oxidative stress. We studied the effects of resveratrol (5 µM) on erythropoiesis in vitro from peripheral CD34+ cells of healthy and b-thal subjects. Erythroid maturation was evaluated at 7, 9, 11 and 14 days of culture by cytofluorimetric analysis using the CD71-GPA-CD36 strategy that allows to separate CFU-E, Pro-E, Int-E and Late-Erythroblasts (Merryweather-Clarke AT. Blood 2011). Resveratrol reduced cell growth in both cell types, with a reduction of CFU-E, increased Int-E at day 7 and 9, and increased Int-E and Late-E at 11 and 14 days. The early maturation of erythroid progenitors was confirmed by morphological analysis of the cells. We sorted CFU-E cells (at 7 days) from resveratrol treated and untreated cells and analyzed the cell cycle, cyclinD1 and p21 expression. In both cell types resveratrol induced increased frequency of S-G2/M cells compared to untreated cells with increased p21 [illegible] increased maturation of erythroblasts. No changes of gamma chain [illegible] eratrol (5 µM). Since FOXO3 is a key regulator of erythroid redox required for normal erythroid maturation (Marinkovic D. JCI 2007), FOXO3 expression and activity was assessed in sorted CFU (7day) and Int-E (11 day) with and without resveratrol. FOXO3a mRNA levels were increased in resveratrol treated cells in both sorted cell populations. We used nuclear localization as a surrogate assay for FOXO3a activity and found resveratrol increased the overall expression of FOXO3 protein in the nucleus without impacting significantly the nuclear/cytoplasmic ratio. Interestingly, resveratrol did not appear to modify FOXO1 expression or subcellular localization. These results suggest that resveratrol enhances specifically expression of FOXO3 in human erythroblasts. Dietary resveratrol supplementation (2.4 mg/Kg) was studied in wild-type and $Hbb^{3th+/-}$ mice (2 months of age) for 6 months. In resveratrol $Hbb^{3th+/-}$ treated mice increased Hb levels (8.3±0.6 vs 10.3±0.5 g/dL, *n*=12; P<0.05) and decreased reticulocyte count (33.9±0.8 vs 23.7± 8.2 %, *n*=12; P<0.05) were observed. Significant increased MCV (34.6±0.6 vs 41.6± 5.4 fL, *n*=12; P<0.05) and MCH ( 9.7± 0.6 vs 12.8 ± 2.1 pg, *n*=12; P<0.05) were also noted. Flow cytometric evidence of decreased ineffective erythropoiesis and reduced spleen/ body weight ratio were also observed. These data indicate that resveratrol affects erythroid maturation both in vitro and in vivo, and that these effects have possible therapeutic relevance for the treatment of thalassemias.

**Disclosures: Cappellini:** *Novartis Pharmaceuticals:* Honoraria, Research Funding.

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