COUP-TFII ORPHAN NUCLEAR RECEPTOR IS AN ACTIVATOR OF FETAL γ-GLOBIN

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Red blood cells are essential for life in vertebrates, due to their function in oxygen delivery. The subsequent waves of erythropoiesis during development produce different hemoglobins, in order to meet the oxygenation need of the developing embryo. In adulthood, during erythroid maturation, the production of α- and β-globin chains in the right ratio is critical to form adult hemoglobin. Unbalanced/altered β-globin expression cause severe diseases (β-hemoglobinopathies: β-Thalassemia and Sickle Cell Anemia). Clinical evidence indicates that increasing levels of fetal γ-globin can ameliorate the severity of these diseases. Thus, the understanding of the regulation of the fetal γ-globin expression regulation represents an important clinical goal.

Here we report a novel role of the orphan nuclear receptor Coup-TFII as an activator of γ-globin in different erythroid cells systems. In mouse, Coup-TFII is expressed in early erythropoiesis of yolk sac origin, together with embryonic/fetal globins. Importantly, Coup-TFII overexpression activates the embryonic/fetal globins genes when expressed in adult cells (mouse E13.5 fetal liver proerythroblasts and human peripheral blood cultures from healthy donors and $\beta^0$39 thalassemic patients). Indeed, its overexpression is capable of overcoming the γ-globin repression imposed by the adult erythroid cellular environment. Conversely, the knock-out of Coup-TFII in β-globin K562 expressing cells (β-K562) results in an increase of the β/(γ+β) ratio. Moreover, we confirmed the ability of Coup-TFII to bind to the β-globin locus (ChIP-seq) and to concur to the conformation of the locus (3C-conformation capture experiments).

Our data candidate COUP-TFII as a specific activator of γ-globin. Since a promising strategy for the treatment of β-hemoglobinopathies could be the reactivation of fetal γ-globin expression in patients, ongoing experiments are focused to better characterize the functional role of COUP-TFII (and of its direct and indirect target genes) in the regulation of the hemoglobin switching.