**ID: 156**
**Area di Laboratorio**
***Orale***
*Parole chiave:* Hipoxia Inducible Factor 2, erytroferrone, erythropoiesis

## Serum levels of HIF2α and ERFE in transfused and non-transfused-dependent thalassemic patients

**Elisa Ferro[1], Anna Paola Capra[1], Petronilla Romeo[1], Maria Angela La Rosa[1], Domenico D'Ascola[2], Silvana Briuglia[1], Saverio Alberti[1]**

[1]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University Hospital of Messina, Italy.; [2]U.O.C. Centro Microcitemia, Riuniti Hospital, Reggio Calabria, Italy; ferro_elisa@alice.it, annapaolacapra@gmail.com, malarosa@unime.it

Introduction. Hipoxia Inducible Factor 2 (HIF-2) has emerged as a regulator of intestinal iron absorption but it indirectly regulates hepcidin suppression through the EPO-mediated stimulation of erythropoiesis (1, 2). Erytroferrone (ERFE) was identified as the major negative regulator of hepcidin in conditions of stress or ineffective erythropoiesis (3).

Phlebotomy or EPO administration in ERFE-knockout mice failed to suppress hepcidin, demonstrating that ERFE is absolutely necessary for acute hepcidin response to increased erythroid activity. Recently, has been developed the first-generation assay for human ERFE (hERFE) proving the pathological increases of ERFE with a parallel decrease of hepcidin in β-thalassemia patients (4).

Objectives. We aimed herein to determined serum levels of HIF2α and ERFE in transfused and non-transfused-dependent thalassemic patients (NTDT) in relation with others anemia and erythropoiesis parameters. Was also evaluated the effect of splenectomy and their fluctuation over the inter transfusion interval between pre- and post-transfusion sampling time.

Methods. 20 transfused-dependent (TDT) patients samples were collected just before blood transfusion (T0) and 4/6 days after transfusion (T1) when erythroid suppression was expected to be maximal. In addition were recruited also 24 NTDT and 20 healthy controls.

In TDT group the 50% of patients were splenectomized while in NTDT were 29.16%. Were determined ERFE and HIF-2α using ELISA kits following the recommended protocol. In addition, were determined hemocromocytometric and iron parameters, soluble transferrin receptor factor (sTfR), erytropoitin (EPO) and martial indexes, fetal hemoglobin (HbF) ratio and nucleated red blood cells (NRBC%), a marker of ineffective erythropoiesis.

Results. Serum levels of ERFE and HIF-2α were strongly correlated (R=0.70, P<0.001), both were significantly higher in thalassemic patients than controls group (P<0.001) and in NTDT than TDT patients (P<0.001). In the latter were detected significant fluctuations between T0 and T1 sampling time (P<0.001). In addition, both were not affected by splenectomy and were observed several relationships with other determined parameters. We confirmed that ERFE was strongly correlated to EPO and we described a new interaction with sTfR (P=0.007).

Discussion. As recently reported by Ganz (4), our patients had higher ERFE levels than controls with lower values in TDT compared to NTDT subjects. We confirmed this results also by higher HIF-2α levels in NTDT than TDT patients and by its fluctuation between pre and post-transfusion time in TDT group. Both ERFE and HIF2α levels abruptly decreased within 4/6 days and were related to total amount of RBCs transfused required to maintain Hb levels between 9.5 and 10 g/dl. Furthermore, high ERFE levels were associated to low inter-transfusional interval. Measurement of these indices could assist clinical monitoring.

References

1)Mastrogiannaki M, Matak P, Mathieu JR, et al. «Hepatic hypoxia-inducible factor-2 down-regulates hepcidin expression in mice through an erythropoietin-mediated increase in erythropoiesis.» Haematologica., 2012 , 97,827-34.

2)Mastrogiannaki M, Matak P, Peyssonnaux C. «The gut in iron homeostasis, role of HIF-2 under normal and pathological conditions.» Blood, 2013 , 122, 885–892.

3)Kautz L, Jung G, Valore EV, et al. «Identification of erythroferrone as an erythroid regulator of iron metabolism.» Nature Genetics, 2014, 46,678-684.

4)Ganz T, Jung G, Naeim A, et al. «Immunoassay for human serum erythroferrone.» Blood, 2017, 130,1243-1246.