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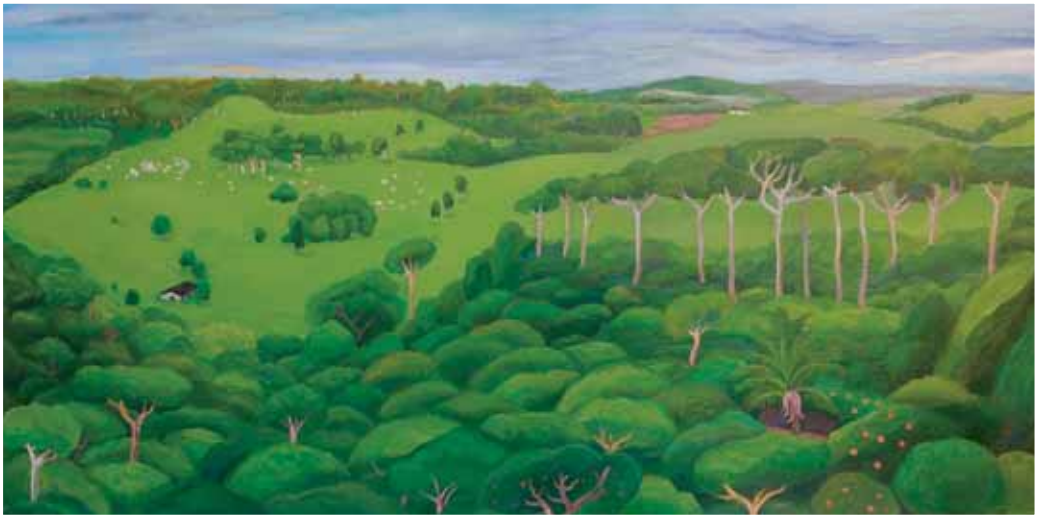

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REUNIÓN CONJUNTA SAIC SAI SAFIS 2018

LXIII REUNIÓN ANUAL DE LA

SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

LXVI REUNIÓN ANUAL DE LA

SOCIEDAD ARGENTINA DE INMUNOLOGÍA (SAI)

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CON LA PARTICIPACIÓN DE

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ASOCIACIÓN ARGENTINA DE NANOMEDICINAS (NANOMED-ar)

14-17 de noviembre de 2018
Hotel 13 de Julio – Mar del Plata

EDITORES RESPONSABLES

Claudia Pérez Leirós
Pablo Baldi
Alberto Crottogini

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JOINT MEETING SAIC SAI SAFIS 2018

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RESPONSIBLE EDITORS

Claudia Pérez Leirós
Pablo Baldi
Alberto Crottogini

multaneous treatment with erythropoietin (Epo). Based on this, we were interested in investigating the mechanisms involved. Migration of endothelial EAhy.926 cells induced by TNF-α was enhanced by the interaction of Epo+TNF-α, despite no effect of Epo alone was detected at 10 IU/mL (E vs. ET, P<0.001, ET vs. T, P<0.01, n=7). Initially, we found an increased expression of TNF-α and Epo receptors induced by the proinflammatory cytokine. Since scratching assays showed a decreased effect of Epo+TNF-α in the presence of an antioxidant (NAC) (ET vs. ETN, P<0.01, n=7), we then analyzed whether reactive oxygen species (ROS) could be involved (flow cytometry; Gm: C 296±25, T 336±20, E 271±32, *ET 465±29, ETNac 312±7, *P<0.001 vs. E and ETNac, n=8). Given that the increased effect of Epo in the presence of TNF-α may be associated to Epo signaling deregulation, we assessed the participation of the tyrosine phosphatase PTP1B. Compared with Epo alone, the combination of TNF-α and Epo decreased phosphatase activity (a.u.: C 0.5±0.1, T 2.5±0.1, E 9.4±2.4, *ET 1.0±0.5; *P<0.01 vs. E, n=3), and expression of PTP1B (flow cytometry, Gm: C 2424±103, T 2632±285, E 3524±225, *ET 2751±302, *P<0.05 vs. E, n=5).
The results suggest that the oxidative stress generated by the inflammatory environment may cause PTP1B inactivity, therefore increasing the period of cell activation by Epo, justifying the stimulatory action of Epo on the migratory effect of TNF-α.
The proangiogenic ability of proinflammatory factors, enhanced in the presence of erythropoietin, might favor the action of this growth factor as a vascular protectant in ischemia.

646. (729) **EFFECT OF ERYTHROPOIETIN IN BRONCHIAL CELLS IN AN IRON EXCESS MOUSE MODEL.**
Maria Florencia Fernandez Delias, Marta Roque
INBIOSUR, Depto. De Biología, Bioquímica y Farmacia, Universidad Nacional del Sur

Imbalances of iron homeostasis are implicated in acute and chronic lung diseases. However, the mechanisms involved in pulmonary iron deposition and its role in the pathogenesis of lung diseases remains unknown.
The aim was evaluate the effect of erythropoietin on bronquial cells in an iron excess mouse model studying the regulatory proteins of the iron cycle CF1 mice(25±5g; 3 months-old) were divided into 4 groups(n=4/group):1)Control; 2)Iron-overload(iron saccharate;-days0,4,8,12 ip;1800mg/kg); 3)EPO(days17,18,19) ip;20000UI/kg);4)Iron-overload+EPO. Immunohistochemistry: anti-prohepcidin, L-ferritin, DMT1(divalent metal transporter1) and ZIP14(Zrt-Irt-like Protein14) followed by Perl´s staining. The Protocol was approved by the CICUAE; UNS.
We observe that the DMT1 localization in bronchial cells was cytoplasmatic in iron overload+EPO, control and EPO while in overload the importer was in the apical zone and in membrane cells.
ZIP14 expression in bronchial cells was evident in iron overload while it was slight iron overload+EPO, control and EPO.
In control and EPO hemosiderin was absent while in Iron overload and iron overload+EPO it was abundant in alveoli.
The L-ferritin expression in iron overload was intense in alveoli and apical in bronchial cells. However it expression in iron overload+EPO was cytoplasmic in bronchial cells. It expression was slight in alveoli and cytoplasmatic in bronchial cells of control and EPO.
The prohepcidin expression was similar in all conditions.
The decrease of ZIP14 expression, and the change in the DMT1 and L-ferritin localization in Iron overload+EPO compared to iron overload, could be reflecting a lower iron uptake and storage in bronchial cells in EPO presence, suggesting a protective mechanism EPO-DEPENDENT.

647. (490) **INVOLVEMENT OF HOMOCYSTEINE AND ADENOSINE IN ERYTHROPOIETIN RESISTANCE IN HUMAN ERYTHROLEUKEMIA CELLS**
Agustina Schiappacasse, Chamorro María Eugenia, Romina Maltaneri, Alcira Nesse, Daniela Vittori
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End Stage Renal Disease (ESRD) is associated with the anemia detected in inflammatory conditions, and negative prognosis arises when hiperhomocysteinemia (HHcy) and accumulation of adenosine (Ado) enhance TNF-α cytotoxicity. Previously, we found that the presence of Ado and Hcy increased the sensitivity of undifferentiated erythroleukemia K562 cells to TNF-α-induced apoptosis, which could not be prevented by erythropoietin (Epo). In this study, we investigated whether differentiated cells could be protected by Epo in an inflammatory environment with Hcy and Ado accumulation. Cells were pre-treated with Epo (10 U/mL, 2 h) and differentiated with hemin (C, 30 μM, 48 h). Hcy (500 μM), Ado (250 μM) and TNF-α (T, 30 ng/mL) were added in the last 24 h of differentiation. Contrary to our observations in undifferentiated cells, Epo prevented TNF-α-induced apoptosis (Hoechst staining: C 17.1±0.9; *T 33.9±1.6; *EpoT 25.2±0.5; *EpoHcyAdoT 35.0±1.5,*P<0.05, n=8). The higher sensitivity of these cells to TNF-α could be explained by a lower expression of c-FLIP (caspase 8 inhibitor, Real-Time PCR). However, Epo was unable to protect the cells against the proinflammatory cytokine when Hcy and Ado were present. We propose that mitochondrial depolarization is involved, since the mitochondrial membrane potential was lower in treatments with Hcy and Ado than in assays in the absence of these compounds (MitoTracker dye, MMP: C: 13.8±2.2%; *ET: 13.5±1.8 *EHcyAdoT 7.6±0.5%, *P<0.05, n=5).
In conclusion, unlike the behaviour of undifferentiated cells, erythroid differentiation increases the sensitivity of K562 cells to TNF-α, which can be prevented by Epo. However, this protective effect of Epo is inhibited when Ado and Hcy are present. This may represent a new explanation for the resistance to human recombinant erythropoietin treatment observed in patients with anemia and hyperhomocysteinemia.

648. (736) **INTEGRATIVE RESPONSE OF IRON CYCLE PROTEINS BY IRON EXCESS IN NEUROBLASTOMA CELLS.**
Maria Florencia Fernandez Delias, Gisela Giorgi, Marta Roque
INBIOSUR, Depto. De Biología, Bioquímica y Farmacia, Universidad Nacional del Sur

Many of the known neurodegenerative diseases have been shown to be influenced by changes in brain iron. Unlike other diseases where the association with iron metabolism has been established, the link between iron and neurodegenerative diseases remains unclear The aim of this study was study the iron effect in neuroblastoma cells(SH-SY5Y) evaluating the expression of iron cycle proteins,ZIP14(Zrt-Irt-like Protein14), DMT1 (divalent metals transporter1) and TfR1(Transferrin receptor1)(importers); H/L-ferritin(storage) and prohepcidin(regulatory protein).
The cellular viability was observed by a dose-response curve (neutral red) with low(30-80μM) or high(200-600μM) FAC(ferric ammonium citrate) concentrations. Iron cellular uptake was measured in the culture medium of cells treated with FAC30μM/72hs and 600μM/24hs(FerColor kit). In cells treated with FAC30μM/72hs and/or pretreated with NAC(N-acetylcystein)2mM/12hs the proteins expression and localization were determinated by immunocytochemistry and immunofluorescence.
The cellular viability decreased in cells incubated 72hs and 24hs with low or high FAC concentrations(p<0,05). Iron uptake was confirmed by its reduction in the culture medium (25%FAC600μM/24hs;42%-FAC30μM/72hs). ZIP14,prohepcidin,H/L-ferritin expressions were intense in SH-SY5Y+FAC respect to the control. DMT1 immunoexpression was lower in SH-SY5Y+FAC than control. In SH-SY5Y+NAC+FAC the change in the expressions of our studied proteins induced by iron were reversed by NAC pretreatment.
TfR1 was in the cellular membrane and cytoplasmatic in basal conditions and only cytoplasmic in FAC presence.The colocalization of TfR2 and HFE was restricted to FAC presence.
The increase of the storage proteins H/L-ferritin evidence the SH-SY5Y cells ability to uptake iron from the extracellular medium, it could explains by the change of TfR1 location (internalization) and the increase in ZIP14 expression.
These iron importers could be the responsible for the neuronal death induced by oxidative stress being the importer DMT1 a minor rol.