Inmunología, patología vascular y trombosis

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Clínica Universidad de Navarra
• Hemostasis and thromboinflammation
• Immunothrombosis- a double edged sword: immune defense vs damage of the host
• Leukocytes as inciters of thrombosis beyond microbian protection
• NETs and vascular pathologies
• NETs and liver disease
The hemostatic system in vivo
Thromboinflammation: an important pathogenic process linked to a diverse range of human diseases

Jackson SP. Blood 2019
Venous thrombosis as an inflammatory process
Proinflammatory and prothrombotic function of inflamed endothelial cells

Jackson SP. Blood 2019
Regulation of immune cell function by platelets
First description of the generation of NETs
Retention of pathogens by immunothrombosis: Recognition, containment and destruction
Composition of NETs
Immunothrombosis
Neutrophils as prominent drivers of vascular inflammation
Nucleosomes and DNA in sepsis

Gould TJ. Arterioscler Thromb Vasc Biol 2014
DNA and nucleosomes in patients with DVT

Diaz JA. J Vasc Surg Venous Lymphat Disord 2013
van Montfoort ML. ATVB 2012
NETs and thrombosis
Acute Ischemic Stroke

- Stroke is a leading cause of death and long-term disability worldwide
- Only two options available
  - Pharmacological thrombolysis with tPA
  - Endovascular thrombectomy

Large Vessel Occlusion (LVO)

Histological analysis of the thrombus
NETs and thrombosis in stroke patients

Clinical data
- Revascularization
- Neurological Scales
- Mortality 90 days

Immunohistochemical analysis
- NETs (NE & Citrullinated H3)
- TAFI
- MMP-10
- FXIII

LVO n = 45

New biomarkers
- NETs and thrombosis in stroke patients

New pharmacological targets

Data Integration & Analysis

Navarro M. ISTH 2019
<table>
<thead>
<tr>
<th>LVO patients characteristics</th>
<th>n = 45</th>
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<tbody>
<tr>
<td>Age</td>
<td>70.13 ± 10.89</td>
</tr>
<tr>
<td>Sex (women)</td>
<td>25 (47.2)</td>
</tr>
<tr>
<td>HTA</td>
<td>27 (60)</td>
</tr>
<tr>
<td>Glucose</td>
<td>121.38 ± 33.82</td>
</tr>
<tr>
<td>NIHSS basal</td>
<td>16.74 ± 5.17</td>
</tr>
<tr>
<td>NIHSS 90 days</td>
<td>3.46 ± 5.49</td>
</tr>
<tr>
<td>mRs basal</td>
<td>0.52 ± 0.77</td>
</tr>
<tr>
<td>mRs 90 days</td>
<td>3.15 ± 2.09</td>
</tr>
<tr>
<td>Mortality 90 days</td>
<td>12 (26.1)</td>
</tr>
<tr>
<td>Complete Recanalization(TICI 2b or 3)</td>
<td>37 (82.2)</td>
</tr>
</tbody>
</table>

Quantitative variables: Mean ± SD
Categorical variables: n (%)
Citrullinated H3

Spearman

R = 0.333

p = 0.028

Complete Recanalization

Navarro M. ISTH 2019
Mortality 90 days

\[ p = 0.032 \]

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE (%) Citrullinated H3 (%)</td>
<td></td>
</tr>
</tbody>
</table>

**Spearman**

R = 0.333

\[ p = 0.028 \]

**Navarro M. ISTH 2019**
The implication of NETs in numerous pathophysiological conditions

- Atherosclerosis
- Arterial thrombosis
- Venous thrombosis
- Cancer
- Diabetes mellitus
- Autoimmunity
- Alzheimer’s disease
- Preeclampsia
- Transfusion-related acute lung injury
- Allergic asthma
- Gout
- Sickle-cell disease

Resting neutrophil → Activation → Activated neutrophil → NETs
NETs and liver disease
Liver Transplantation 2018; 24:1716

Gitrullinated Histone H3: Early Biomarker of Neutrophil Extracellular Traps in Septic Liver Damage
Kozo Nomura, MD,1,9 Tomoharu Miyashita, MD, PhD,5,6 Yasutake Yamamoto, MD, PhD,6 Seiichi Muniesue, PhD,6 Akira Harashima, PhD,1 Hideo Tsuchiya, PhD,1 Sachio Fushida, MD, PhD,1 and Tetsuo Ohta, MD, PhD1

Elevated Plasma Levels of Cell-Free DNA During Liver Transplantation Are Associated With Activation of Coagulation
Fien A. von Meijenfeldt,1,2 Laura C. Barlage,1,2 Sarah Bou,1,2 Jelle Adelmeijer,1 Robert J. Porte,2 and Tim Lisman1,2

Neutrophil Extracellular Traps Promote Inflammation and Development of Hepatocellular Carcinoma in Nonalcoholic Steatohepatitis
Dierk J. van der Windt,9 Vikas Sud,1 Hong Zhang1, Patrick R. Verley,1 John Gerevin,1 Hanna O. Yudkin,1 Susan Tobin,1 Patricia Loughran1, Robert M. O'Doherty1, Mark E. Moreira,1 Hui Huang1,1 Richard L. Stratton1, and Alan Tong1

Impaired neutrophil extracellular traps and inflammatory responses in the peritoneal fluid of patients with liver cirrhosis
Juan Manuel Agraz-Cibrián1,2,3 | Vidul Delgado-Ríz1 | Jorge Enrique Segura-Ortega4 | Héctor Alfredo Maldonado-Gómez1 | José Francisco Zambrano-Zaragoza1,2 | Ma. de Jesús Durán-Avelar1 | Norberto Víbancos-Pereira2 | Mary Faffitis-Morris2

Abnormal neutrophil traps and impaired efferocytosis contribute to liver injury and sepsis severity after binge alcohol use
Terence Ndongy Bukong1,2,3, Yeomhee Cho1, Arvin Iracheta-Vellve1, Banisheer Saha1, Patrick Love1, Adeyinka Adejumo1, Istvan Furii1, Aditya Ambade1, Benedek Gyongyoss1, Donna Catalan01, Karen Kody1, Gyongyi Szabo1,2,3

Research Article
Genetic and Metabolic Diseases

HUMAN IMMUNOLOGY

JOURNAL OF HEPATOLOGY
Molecular links between coagulation and innate immunity: role of complement

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Email: ed.conway@ubc.ca
NETosis, coagulation and complement: a triangular relationship
Therapeutic modulation of coagulation processes in sepsis

Jackson SP. Blood 2019
Neutrophil Extracellular Traps: A New Therapeutic Target?

Circulating DNases prevent vascular occlusion by neutrophil extracellular traps

Tobias A. Fuchs PhD

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