

**Gender differences in the plasma concentration of the GAS6-TAM system in COVID-19 patients.**

A. Morales<sup>1</sup>, S. Rojo Rello<sup>2</sup>, H. Cristóbal<sup>1</sup>, A. Fiz-López<sup>3</sup>, E. Arribas<sup>3</sup>, M. Marí<sup>1</sup>, A. Tutusaus<sup>1</sup>, P. de la Cal-Sabater<sup>3</sup>, N. Martínez-Bosch<sup>4</sup>, M. L. Sorlí<sup>5</sup>, J. Gomez-Junyent<sup>5</sup>, P. Navarro<sup>1</sup>, G. A. Nicolaes<sup>6\*</sup>, J. T. Ortiz-Pérez<sup>7</sup>, D. Bernardo<sup>3</sup>, P. Garcia De Frutos

<sup>1</sup>Cell Death and Proliferation, Institute of Biomedical Research of Barcelona (IIBB-CSIC), Barcelona, <sup>2</sup>Servicio de Microbiología, Hospital Clínico Universitario de Valladolid, <sup>3</sup>Mucosal Immunology Lab, IBGM-CSIC, Universidad de Valladolid, Valladolid, <sup>4</sup>Cancer Research Program, Hospital del Mar Research Institute (IMIM), <sup>5</sup>Infectious Diseases Department, Hospital del Mar-IMIM, Barcelona, <sup>6</sup>Department of Biochemistry, CARIM, Maastricht University, Maastricht, <sup>7</sup>Clinic Cardiovascular Institute, Hospital Clinic Barcelona, Barcelona, Spain

**Background:** SARS-CoV-2 induces an immune response with potentially harmful effects for the patient due to an uncontrolled release of inflammatory factors, specially at the capillary wall. The vitamin K-dependent plasma protein GAS6 and the TAM (TYRO3, AXL, and MERTK) receptors play a relevant role among restorative mechanisms that counterbalance pro-inflammatory responses at the endothelial interface.

**Aims:** To study the influence of gender on the effects of SARS-CoV-2 infection in the GAS6/TAM system, as reflected by plasma concentration at patient admittance at the emergency ward.

**Methods:** The plasma content of GAS6, AXL, and MERTK was analyzed in a first group of 132 patients, 68 females and 64 males consecutively admitted to the emergency ward during the first peak of COVID-19. A confirmatory group was studied from the second wave of contagions. An analysis of gender differences in relation to the GAS6/TAM concentrations in plasma was performed on this population.

**Results:** In accordance with recently published GAS6 levels, significantly higher in the SARS-CoV-2 positive than in negative patients, increased progressively with the severity of the disease in SARS-CoV-2 positive individual irrespective of the gender of the patient. In contrast, while soluble AXL exhibited higher plasma concentration in deceased patients and no significant differences were observed in MERTK concentration, differential gender analysis suggest differences in soluble TAM receptors. While a COVID-19 related increase in sAXL was observed in men, this was not the case in women. Oppositely, MERTK differences due to COVID-19 infection were only significant in women.

**Summary/Conclusion:** GAS6-TAM system of ligands and receptors is implicated in the immune response to SARS-CoV-2 in patients from both genders. Plasma GAS6 levels paralleled COVID-19 severity being an early marker of disease prognosis in both sexes. In contrast, soluble TAM receptors presented a gender-specific behavior. Sex-related differences in sAXL and sMERTK expression in COVID-19 patients could affect therapy efficacy deserving further investigation.