UNIVERSITATEA TITU MAIORESCU DIN BUCUREȘTI
FACULTATEA DE MEDICINĂ
IOSUD – Domeniul Medicină

ABSTRACT

Habilitation Thesis

"Interactions between hemostasis, immunology and pregnancy: from pathogenesis to personalized therapy"

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The habilitation thesis entitled "Interactions between hemostasis, immunology and pregnancy: from pathogenesis to personalized therapy" synthesizes my scientific research and professional activity conducted at the intersection of hematology, hemostasis, and reproductive immunology.

The foundation of my research was the clinical observation of the high prevalence of thrombotic events in patients with Philadelphia-negative chronic myeloproliferative neoplasms, particularly in those carrying the JAK2 V617F mutation. This somatic mutation, involving the substitution of valine with phenylalanine at position 617 in the pseudo-kinase domain of the JAK2 protein, leads to constitutive activation of the JAK-STAT signaling pathway, inducing not only uncontrolled proliferation of myeloid cell lines but also significant changes in platelet functionality, blood rheological properties, and the molecular phenotype of the vascular endothelium.

The doctoral study, conducted on a cohort of 192 patients with chronic myeloproliferative neoplasms, enabled detailed characterization of the thrombotic profile associated with the JAK2 V617F mutation and identification of distinct patterns of thrombotic manifestations according to mutational status. Research demonstrated that thrombotic risk is determined by a complex constellation of interconnected factors, including mutant allele burden level, intrinsic platelet activation, endothelial dysfunction, and interaction with concomitant hereditary thrombophilias.

A contribution was the analysis of the synergistic effect of the association between JAK2 V617F mutation and hereditary thrombophilias on thrombotic risk, demonstrating that patients with both genetic factors present a significantly higher risk of thrombotic events compared to those with isolated JAK2 V617F mutation. I developed a conceptual model

explaining the interaction between the presence of JAK2 V617F mutation and hereditary thrombophilias, with direct implications for risk stratification and personalization of preventive interventions.

Clinical observations regarding the increased frequency of obstetric complications in patients with myeloproliferative neoplasms and JAK2 V617F mutation generated a new research direction. Investigating the relationship between genetic thrombophilias and reproductive pathology, I found that the presence of JAK2 V617F mutation represents an independent risk factor for multiple obstetric complications. However, seeking to understand whether pregnancy losses are explained exclusively by thrombotic mechanisms, I came to explore the immunological component of reproductive pathology.

Thus, my research expanded toward systematic exploration of the role of KIR receptors expressed by uterine NK cells and their interactions with HLA-C molecules at the trophoblast level. The data obtained indicated that certain combinations of maternal KIR genotypes and fetal HLA-C are associated with deficient trophoblastic invasion and inadequate remodeling of uterine spiral arteries. Studies explored the involvement of NK cell dysfunctions and cytokine imbalances in recurrent miscarriages and vascular-placental complications, as well as the impact of immunomodulatory treatments on live birth rates in patients with increased obstetric risk.

Contributions in the field of hematological malignancy immunology included studies on immune evasion mechanisms, cytokine profile in immune thrombocytopenia, and HLA-cytokine interactions in response to targeted therapies. I analyzed the management of infectious complications in hematology, the role of intestinal microbiota, and infectious risk associated with targeted therapies. Additionally, I studied the impact of the COVID-19 pandemic on patients with hematological neoplasms, identifying prognostic factors and analyzing specific complications such as Long COVID syndrome and rhino-cerebral mucormycosis.

Professional activity materialized in the position of Head of Clinical Hematology Section I at Colentina Clinical Hospital and the establishment of Smart Clinic in 2016, a framework for applying an integrative approach in the management of recurrent miscarriage and high-risk pregnancies. Scientific output includes 15 articles as principal author in ISI-indexed journals, 12 contributions as co-author, and 4 published books. The Hirsch index is 8 on Web of Science and 11 on Google Scholar. Collaborations with international centers such as Ludwig Institute for Cancer Research and Hôpital Universitaire Necker contributed to the international visibility of the research.

Teaching activity at Titu Maiorescu University includes Hematology courses for the 6th year, for General Medicine and Medicine in English students, the optional course on Regenerative Therapy with Stem Cells, coordination of undergraduate theses, and supervision of residents. I initiated the Scientific Circle of Hematology for Residents to develop critical reading skills and evaluation of scientific evidence.

Future research directions will continue to explore interactions between hemostasis, immunology, and reproduction, with a focus on personalized medicine. Collaboration with international centers for research in the field of clonal hematopoiesis, exploration of the role of circulating microRNAs as predictive biomarkers, and characterization of the epigenetic profile in obstetric context constitute priorities for the upcoming period. Long-term objectives include the development of educational programs, expansion of the Scientific Circle of Hematology at the national level, and coordination of doctoral students in fields such as reproductive immunology and thrombophilias.