PROGETTO

Supervisore::	**Simone Cenci**
Titolo	**Deciphering and Targeting VEXAS**
Curriculum:	**Biologia Cellulare e Molecolare**
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/genetics-and-cell-biology/age-related-diseases/simone-cenci.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/Lacune di conoscenza

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome (1/4,000 males aged >50) is a novel, adult-onset, severe, hemato-inflammatory disease due to clonal dominance of hematopoietic cells bearing a somatic mutation in the UBA1 gene, encoding a key enzyme of the ubiquitylation cascade (1). VEXAS presents with systemic inflammation and hematologic abnormalities. Current therapies are poorly effective and burdened by debilitating side effects. VEXAS mutations inactivate cytoplasmic UBA1-driven ubiquitination, impairing protein clearance and triggering stress responses (2,3). Exploiting our novel *in vitro* and *in vivo* VEXAS models and patient-derived samples, we demonstrated that healthy hematopoiesis in VEXAS is poisoned by a detrimental inflammatory milieu leading to dominance of inflammation-resilient UBA1-mutant clones (4). Mechanistically, mutant HSPCs display heightened Unfolded Protein Response (UPR), which may sustain inflammatory programs and contribute to pro-survival mechanisms, coupled to dysregulated autophagy, which may explain the observed resilience to an inflamed niche by favoring adaptive dynamics (5,6).

Razionale e ipotesi

Despite the identification of *UBA1* mutations as the genetic driver of VEXAS syndrome, the mechanisms linking somatic mutation, inflammation, and clonal dominance remain poorly understood, limiting therapy development. Deciphering these mechanisms might reveal predictive markers, actionable targets, and inform drug repurposing or novel therapies.
Building on our previous findings (4), we hypothesize that cell-intrinsic and -extrinsic mechanisms triggered by altered UBA1 function and by its impact on protein and organelle homeostasis are key and targetable drivers of the relationship between inflammation and clonal dominance in VEXAS. In particular, impaired degradation of proinflammatory mediators, heightened UPR, and deregulated autophagy in mutant HSPCs may sustain inflammatory programs and afford pro-survival mechanisms in the inflamed BM, promoting clonal dominance.

Obiettivi e finalità specifiche

The proposal aims to achieve the following specific objectives:
1) Identify and dissect, in our *in vitro* VEXAS models, cell-intrinsic and -extrinsic pathological mechanisms triggered by altered UBA1 function, driving inflammation and clonal advantage of UBA1 mutant cells;

2) Confirm these mechanisms by characterizing BM and peripheral hematopoietic cells from VEXAS patients;
3) Validate the identified mechanisms in VEXAS *in vitro*/*in vivo* models, as well as in patient-derived samples, through targeted pharmacological or genetic modulation. The results will enable to prospectively identify prognostic markers and devise specific and effective therapies against VEXAS.

Risultati attesi

Our research plan is expected to unravel fundamental mechanisms sustaining inflammation and clonal dominance in VEXAS syndrome to prospectively devise new targeted therapies against this cureless disease. The study will critically advance the understanding of VEXAS syndrome through comprehensive dissection and validation of molecular and mechanistic determinants governing the disease pathogenesis and evolution.

Competenze che dovrà acquisire la/il Dottoranda/o(in inglese, max 600 caratteri spazi inclusi)

The candidate will acquire expertise in laboratory techniques including culture and differentiation of HSPCs and immune cells, gene editing, biomolecular and biochemical assays (DNA/RNA extraction, ELISA assays, PCR, western blot analysis), isolation of PBMCs and BMMCs, flow cytometry and microscopy. In addition, the student will develop bioinformatics competencies for the analysis of multi-omics datasets (transcriptomics, proteomics, metabolomics) and will strengthen skills in independent experimental design, data analysis and interpretation, data presentation, and scientific writing

Bibliografia (massimo 15 voci)

1. Beck DB et al., N Engl J Med. 2020
2. Fiumara et al. Curr Opin Rheumatol. 2026
3. Rape M Nat Rev Mol Cell Biol. 2018
4. Molteni R et al., Nat Med 2025
5.Hetz C et al., Nat Rev Mol Cell Biol 2020
6. Ho TT et al., Nature. 2017