RESEARCH TOPIC MECM_9

Mutation Driven Inflammation as a Driver of Cancer Evolution: A Proteomic Discovery Platform in Myeloid Neoplasms and Clonal Hematopoiesis

Curriculum
MECM Standard

Research Area
Onco

Laboratory name
Genomics of Hematological Malignances Lab

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Abstract
Low-risk myeloid neoplasms (LR-MNs) are clinically considered indolent yet consistently linked to reduced survival, systemic inflammation, cardiovascular complications, and a higher likelihood of progression to acute myeloid leukemia. These features show that even "indolent" disease harbors active clones capable of reshaping systemic immunity long before transformation. Despite this, LR-MNs remain underexplored in early-phase therapeutic strategies aimed at preventing clonal evolution.
Clonal hematopoiesis mutations such as TET2, DNMT3A, JAK2 and ASXL1 increase the risk of hematologic cancers, cardiovascular events, and mortality. These lesions promote chronic low-grade inflammation and alter immune-cell behavior, suggesting that inflammatory rewiring is a shared mechanism driving malignant progression. VEXAS syndrome, caused by somatic UBA1 mutations, exemplifies how a single clone can induce systemic autoinflammation, cytopenias, marrow dysfunction, and high mortality. It also highlights the convergence of ubiquitination defects, ER stress, and inflammatory activation, showing how proteotoxic stress in hematopoietic progenitors can propagate immune dysfunction.
Epidemiological studies reveal that UBA1 mutations are more common than expected and frequently coexist with CH mutations, reinforcing the idea that inflammatory phenotypes arise from interactions between somatic genetics and immune remodeling. Mechanistic work shows that UBA1 dysfunction activates the unfolded protein response, disrupts E2 enzyme charging, and triggers cytokine release, linking proteostasis failure to inflammation.
A major unmet need is a systematic proteomic and inflammatory atlas of circulating immune cells across LR-MN genotypes. These cells act as sentinels of early malignant evolution, integrating signals from mutant stem cells, systemic inflammation, and microenvironmental stress. Mapping their proteomic signatures will clarify how mutation-specific inflammatory programs remodel immunity, promote clonal expansion, and create permissive niches for malignant progression. The project will deliver a ranked list of druggable targets suitable for early intervention strategies.

Main technical approaches

Multi-parameter flow cytometry. Cell colture. Nucleic acid purification and quantification. RNA/DNA library preparation. R or Python proficency .

Scientific references

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Type of contract

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