

Single-Cell Profiling Identifies a NAMPT-Centered Inflammatory Program Implicated in the Cardiovascular Toxicity of GnRH Agonist Therapy for Prostate Cancer

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Background. Androgen deprivation therapy (ADT) is central to prostate cancer treatment, yet cardiovascular disease is now a leading competing cause of death among men receiving it. Randomized data show fewer major adverse cardiovascular events with GnRH antagonists than agonists, but agonists remain predominant because of cost, dosing, and drug interactions. The excess risk appears within weeks of starting an agonist, too soon for metabolic change and consistent with an acute immune–vascular mechanism. In the completed REVELUTION-1 trial, the agonist leuprolide produced greater twelve-month non-calcified plaque progression than the antagonist relugolix or radiotherapy alone, and in a retrospective institutional cohort radiotherapy plus an agonist was associated with higher unadjusted cardiac-specific mortality. We hypothesized that GnRH agonist therapy is associated with an immune-mediated endothelial inflammatory cascade, in which circulating monocytes and T cells adopt an activated state that engages the vascular endothelium and resembles the immune profile of acute coronary events.

Methods. We profiled peripheral blood mononuclear cells by single-cell RNA sequencing in ten men with localized prostate cancer on definitive radiotherapy with concurrent leuprolide (CO-PRO cohort), before and six months after starting therapy (19 samples), comparing composition and expression by paired pseudobulk mixed-effects models (FDR<0.05) and confirming Visfatin/NAMPT by flow cytometry. We mapped monocyte ligands to endothelial receptors using a published coronary plaque atlas and compared leuprolide-induced programs by Fisher's exact test with signatures distinguishing ruptured from stable plaque in acute myocardial infarction.

Results. Leuprolide expanded CD14+ and CD16+ monocytes (FDR<0.05). These monocytes upregulated NAMPT and adhesion genes (SELL, CD46, ADGRE5). Cytotoxic CD8+ T cell programs increased (GZMB, GZMH, KLRC2), and RNA velocity showed accelerated naive-to-effector transition. Flow cytometry confirmed more Visfatin+ myeloid cells at month six (p<0.001). Ligand–receptor analysis predicted that monocyte NAMPT and these adhesion ligands engage receptors on coronary endothelium. The leuprolide-induced monocyte program overlapped strongly with plaque-rupture signatures from acute myocardial infarction (293 shared CD14+ genes, OR 4.6, p=5e-52; 105 shared CD8+ effector genes, OR 18.5, p=2e-81), enriched for macrophage and endothelial migration.

Conclusions. Leuprolide is accompanied by a NAMPT-centered inflammatory monocyte program that resembles signatures of plaque rupture and is predicted to act on coronary endothelial receptors. These immune changes arise in the same setting in which leuprolide accelerates coronary plaque progression. Within-patient integration of these signatures with plaque progression is planned using banked REVELUTION-1 specimens and imaging. NAMPT (visfatin), a secreted driver of endothelial activation and leukocyte adhesion, is therefore a candidate druggable target in ADT-associated vascular injury and warrants direct functional testing.

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