Background and Rationale

Monocytes from patients with type 2 diabetes (DM2) and cardiovascular disease (CVD) display proinflammatory behavior such as enhanced cytokine production and vascular wall invasiveness, which promote atherosclerosis. This dysregulation is partly caused by epigenetic reprogramming which can be counteracted by epigenetic drugs.

Apabetalone Mechanism of Action

Apabetalone binds competitively to bromodomains in histone acetylation "readers" termed BET proteins, causing their release from chromatin and downregulation of BET sensitive gene expression.

Study Design

14 Subjects with DM2 and Stable CVD (DM2+CVD) (proIN, D2, D3, unstable angina, TIA, CIK, PAD >3 months wait on Statin and Insulin Therapy) Group 1: 12 Matched Control Subjects

Blood Collection

CD14* Monocytes Isolation
Ex vivo 25 μM Apabetalone or 0.025% DMSO ± 25 U/mL IFNγ

1. Gene Expression Analysis (4h) with NanoString® Luminex Immune Panel (109 genes)
2. Protein Secretion Analysis (24h) with Miliplex® Immuno Profiling (42 cytokines)
3. Bioinformatics with Ingenuity® Pathway Analysis (IPA®) Upstream Regulator Analysis Tool

Summary and Conclusions

- Monocytes from DM2+CVD patients show a hyperactive pro-inflammatory phenotype ex vivo, in non-stimulated and stimulated conditions, despite standard of care therapy.
- Apabetalone reverses this hyperactivation by downregulating key inflammatory genes and secreted cytokines.
- Monocytes from DM2+CVD patients show greater gene sensitivity to BET inhibitor treatment. Data suggests a greater transcriptional dependency of BET proteins in diseased conditions.
- Findings support the development of apabetalone as a therapy for high risk CVD patients with epigenetic dysregulation of the innate immune response.

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