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Trypanosoma cruzi cardiomyocyte infection promotes innate immune response and metabolic rewiring

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Chagas cardiomyopathy is caused by the infection of Trypanosoma cruzi and represents a major etiology for heart failure in Latin America. To understand parasite effects on cardiomyocytes, we infected human iPSC-derived cardiomyocytes with T.cruzi and studied cellular, transcriptomics, proteomics and metabolic responses. Proteomics and Transcriptomics analysis showed infection rapidly activated innate and adaptive immune systems in cardiomyocytes, resembling prototypic responses in pathogen-activated immune cells, and caused a metabolic shift from fatty acid utilization to glycolysis that is dependent on HIF-1α signaling. By probing these responses, we show that parasite uptake is mediated in part by the glucose-facilitated transporter, GLUT4, and that attenuation of glycolysis, HIF-1α activation or GLUT4 expression decreased T.cruzi infection. By contrast, pre-activation of immune responses with LPS resulted in higher infection rates. These observations indicate that T.cruzi exploits a HIF-1α dependent, cardiomyocyte-intrinsic, stress-response activation of glycolysis that promotes intracellular infection and replication and impairs cardiomyocyte physiology and function.

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Chemoproteomic identification of functional microproteins

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Advanced methods in next-generation sequencing and proteogenomics have revealed thousands of previously invisible human protein-coding genes, increasing the known size of the human proteome by at least 10%. This previously unannotated proteomic “dark matter” includes small open reading frames (smORFs) encoding polypeptides of fewer than 100 amino acids, and alternative open reading frames (alt-ORFs) encoding proteins 100 amino acids or larger. Sm/alt-ORFs previously escaped detection due to their short lengths, overlap with annotated protein coding sequences in different reading frames, and/or initiation with non-AUG start codons. Recent studies have shown that hundreds of smORFs are required for cell growth and survival, and some smORF-encoded polypeptides or “micro-proteins” bind to and regulate the activity of macromolecular complexes involved in critical cellular processes and disease. However, distinguishing functional smORFs from spurious translation – or false detections – remains a key challenge, and the functions and phenotypes associated with alt-ORFs that overlap canonical proteins remain almost entirely unexplored. I describe chemoproteomic strategies to profile sm/alt-ORF-encoded microproteins that exhibit functional properties of interest, such as post-translational modifications, regulated translation and subcellular localization. Using these tools, we identified and mechanistically characterized human microproteins that regulate RNA granule formation, inositide signaling and ribosome biogenesis. Chemoproteomic strategies may therefore be lever-aged to accelerate the identification of sm/alt-ORFs with significant biological functions in order to obtain new insights into human cell biology.

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