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Metabolic games: IFI16-driven regulation of cellular metabolism upon HCMV infection

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Introduction. Human cytomegalovirus (HCMV) is associated with acute and chronic disease in both healthy and immunocompromised populations. A critical feature of HCMV is that it modulates the metabolism of an infected cell to favor viral replication. Indeed, HCMV infection has been associated with the increased lipogenesis in infected cells that is likely required for the envelopment of the newly formed virions. However, the fundamental mechanisms responsible for HCMV-induced activation of lipid synthesis remain poorly understood. We have previously reported that interferon- γ -inducible protein 16 (IFI16) is a restriction factor for HCMV and it is delocalized from the nucleus to the cytoplasm as viral escape mechanism.

Methods. To understand if IFI16 interferes with one or more metabolic effects during HCMV infection we generated knockout (KO) gene variants in human foreskin fibroblasts (HFFs) through CRISPR-Cas 9 technology.

Results. Here, we demonstrate that IFI16 reduces the expression of the glucose transporter GLUT4, resulting in decreased glucose import and translocation of the carbohydrate-response element binding protein (ChREBP) to the nucleus. Consequently, reduced transcription of the genes encoding lipogenic enzymes leads to decreased lipid synthesis and enhanced generation of the enveloped viral particles in infected cells.

Discussion and Conclusions. These data may shed light on the potential impact of IFI16 on regulation of glucose and lipid metabolism upon HCMV replication suggesting new promising targets for antiviral therapy.