Regulation of viral infection of prostate cancer cells

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Viral infection is an intricate process that involves an interaction between the virus and its host cell. While viral infection can be a considerable health threat, viruses can also be utilized to our advantage. The overarching goal of my PhD is to unravel some of the molecular mechanisms regulating viral infections, focusing mainly on the infection of prostate cancer (PCa) cells with oncolytic viruses. Initially, following an analysis of prostate cancer (patient-derived and cell lines) gene-expression databases, I focused on Lipocalin 2 (LCN2) as a potential regulator of interferon-based antiviral responses in prostate cancer cells. These studies yielded a novel model in which LCN2-mediated regulation of the eIF2α-branch of the endoplasmic reticulum (ER) stress response, determined the differential susceptibility of prostate cancer cells to the EHDV-TAU oncolytic virus. Having identified this pathway as a central determinant of the infectibility of these cells, I next explored the possibility of direct manipulation of eIF2α activity, as a potential tactic for inhibiting viral infection in cells (cancerous or non-cancerous). This effort was carried out in the context of host-targeted therapy (targeting cellular mechanisms as opposed to targeting viral components), aiming to harness eIF2α-mediated cellular responses to combat viral infection. In particular, I employed GLB7, a derivative of MK28, a novel PERK activator developed by the Lederkremer lab. We investigated GLB7 activity and found that it activates eIF2α in a non-JAK1-dependent manner. Accordingly, GLB7 treatment caused translation arrest in PCa cells, mediated by eIF2α activation. Due to GLB7's inhibitory effects on the translation, and the essentiality of translation to viral replication, we hypothesized that GLB7 should hamper viral infection. We demonstrated that GLB7 administration results in a complete block of viral infection in treated cells in an eIF2α-mediated pathway. These data suggest that GLB7 is an anti-viral drug, functioning through the activation of eIF2α, leading to translation arrest and blocking of viral infection. Together, while the first part of my work focused on the infection of cancer cells as a form of (immuno)therapy, aiming at identifying the molecular underpinnings of differential susceptibility; the second part of my work is a "zoom-out" from the first part, and it focused on

the development of a method by which this same regulatory axis can be harnessed for small-molecule-based anti-viral therapy.