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High-resolution Antibody Profiling of KSHV-infected Individuals Presenting With and Without Kaposi Sarcoma Reveals Distinct Viral-Exposure Signatures

Kaposi sarcoma-associated herpesvirus (KSHV) is a gamma herpesvirus and the etiologic agent of Kaposi sarcoma (KS), an AIDS-defining cancer affecting immunocompromised individuals. Sub-Saharan Africa (SSA) exhibits a particularly high KSHV prevalence. Immune suppression in addition to KSHV infection is thought to drive KS development. However, co-factors such as prior infections may influence pathogenesis or lack thereof. Elucidation of humoral antibody (Ab) repertoire is vital to discern host-pathogen interactions, define detection and prognostic biomarkers, and contribute to vaccine development strategies. Here, we utilized VirScan, a high-throughput phage display library containing 56-mer, overlapping peptide tiles, spanning the entire proteomes of all known human pathogens coupled with phage immunoprecipitation sequencing (PhIP-seq). We identified and quantified Ab responses against 556 viral organisms. Serum samples (n=106) derived from Sub-Saharan Africans stratified to three groups: (1) KSHV seronegative (n=25), (2) KSHV seropositive (n=22), and (3) KS (n=59) were analyzed. Each group is further stratified based on their HIV serostatus. To compare the humoral responses between groups, we quantified the Ab responses based on (1) breadth (sum of significantly enriched, or *reactive* peptides) and (2) magnitude (the frequency of which a reactive peptide is targeted). We explored whether peptide-, protein- and organism-level Ab responses can discriminate between symptomatic disease (KS) and asymptomatic infection (ASY). Overall, comparison of the Ab repertoire indicated that HIV or KSHV infection leads to a less diverse Ab response against viral infections. Specifically, while KSHV infection alone displayed a diminished Ab repertoire relative to uninfected controls, HIV co-infection exhibited diminished repertoire to a greater extent, suggestive of HIV's immunosuppressive qualities, providing an aggregate effect when co-infected with KSHV. Statistical comparison of organism-level breadth between KS and ASY subjects revealed ~30 differentially recognized organisms. We detected significantly higher breadth of Ab responses to hepatitis B, C, and E viruses. Conversely, ASY individuals presented higher breadth against enteroviruses. Focusing on the protein- and peptide-level responses, pattern recognition and network analyses highlighted Ab responses co-occurring with previously reported discriminative KSHV peptides. Thorough proteome annotations and sequence analyses identified clusters of immunodominant proteins and epitopes unique to, or cross-reactive with other viruses. In conclusion, our data elucidated >1,000 peptide-level Ab responses from >50 potential co-infections that discriminate KS from ASY. To validate these peptides and their predictive, prognostic, and therapeutic value, we will analyze these peptides in larger cohorts and longitudinally.