Decoding Host-Pathogen Dynamics with 4D (Epi)Genomics

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The ability to counter biological threats is limited given the enormous lack of knowledge of host resiliency mechanisms in the face of pervasive pathogens. The resilience of multicellular hosts (e.g., plants, animals, and humans) is predicated on the susceptibility of individual cells and effective defense mechanisms to halt the spread of infection for pathogen elimination. Recent work in the field of epigenomics suggests that epigenetics play a key role in host defense. Epigenetic mechanisms collectively function to open or close regions of chromosomes to control gene expression. The resulting dynamic structural changes in the genome underpin most biological functions, including responses to infection. Conversely, genome structure can be altered by pathogens to reorient host cellular function to enhance pathogen replication or to establish latent or persistent infections. In response, hosts employ epigenetic modifications to counter infection, thereby altering the expression and 3D spatial configuration of their own genomes. *The team hypothesizes that epigenetic modifications vary between resilient vs. susceptible host cells and that underlying changes to the epigenome and genome are characteristic of pathogen classes.* Although recent progress has been made, scientists and decision makers currently lack methods to quickly compare and identify these pathogen-induced changes to host genomes to understand susceptibility and resiliency. The team proposes to address this gap by taking a holistic, 'one health' approach to (1) develop an experimental workflow to characterize and survey early onset molecular signatures of infection found in the genome and epigenome; (2) leverage ASCR user facilities to create an exascale computational and explainable artificial intelligence (XAI) workflow that integrates this data (and data from the user community) to enable interactive, comparative 4D (3D + time) (epi)genome exploration and predictive dynamic modeling; and (3) integrate 3D genomic structural maps, epigenetic modifications, and ultra-resolution physical images (using Cryo-EM) to validate genome structure:function relationships. This platform is agnostic by design and can be adapted for any pathogen (e.g., bacteria, fungi, viruses). Herein, researchers will first apply this platform to examine viral infection(s) in mammalian and plant systems to determine (for the first time) realistic 3D spatial architecture and dynamic reconfigurations of key host genomes induced by viral pathogens. Broad knowledge of epigenetic regulation of host-pathogen interactions would greatly advance the ability to predict pathogens that have high potential to cause the next global scale catastrophe or pandemic and will directly advance genomics capabilities in biopreparedness to transform the nation's ability to prepare for, and respond to, future biological threats.