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G4-KuRE - Roles of G-quadruplexes in Kaposi's sarcoma-associated herpesvirus latent REplication

Kaposi's sarcoma-associated herpesvirus (KSHV) is a widespread oncogenic virus, whose infection can cause Kaposi's sarcoma, an incurable cancer frequent in immunocompromised individuals. Similar to other herpesviruses, KSHV establishes a latent infection in the host, characterized by lifelong persistence of the viral genome. Necessary and sufficient for latent infection are the virally expressed latency-associated nuclear antigen (LANA) and highly repetitive GC-rich sequences on the viral genome, named terminal repeats (TRs). While several studies have uncovered the importance of LANA in promoting KSHV DNA replication and segregation during latency, the essential role of the TRs remains poorly understood. In particular, the GC-rich regions contained in the TRs have been speculated to fold into G-quadruplexes (G4), secondary DNA structures that can function as replication barriers, but their roles remain elusive. A deep mechanistic understanding of the ways KSHV maintains itself in latency would be crucial to uncover a way to eradicate the virus from the infected cells, before the onset of Kaposi's sarcoma, but this knowledge is missing, mainly due to the methodological limitations of investigating KSHV latent replication solely in cells. With this proposal, I aim to take advantage of the *Xenopus laevis* egg extract in vitro system to go beyond such limitations and to gain mechanistic insight in the role of G4s in the latency of KSHV. By combining my extensive expertise in the field of DNA replication with the deep knowledge of Prof. Sara Richter at the University of Padua in secondary DNA structures in viral genomes, I aim at mechanistically defining the strategies adopted by KSHV to maintain itself in latency and at identifying approaches to prevent viral maintenance in KSHV infected cells. The proposed project will have great societal impact on cancer prevention, and it will be pivotal for my scientific and personal growth into an independent junior group leader.

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