Impact of SARS-CoV-2 Alpha and Omicron variants on Golgi apparatus organization and architecture in cardiomyocytes.

Since its emergence in late 2019, SARS-CoV-2 has caused over 7 million deaths worldwide, with approximately 776 million cases reported [1]. Although primary infection is established in respiratory cells, SARS-CoV-2 can also replicate in other cell types such as neuronal cells [2], intestinal cells [3] and cardiac cells. Infection of cardiomyocytes leads to cardiac complications such as arrhythmias, heart failure and elevated cardiac stress biomarkers [4].

Studying the pathogenic mechanism behind cardiac lesions in patients infected with SARS-CoV-2 is a first step towards the development of therapeutic strategies to treat cardiomyopathies induced by this virus. Recent advances in the conversion of human induced pluripotent stem cells (HiPSCs) have enabled the large-scale production of patient-specific cells, including HiPSC-derived cardiomyocytes (HiPSC-CMs) [5]. These cells mimic the cellular phenotypes of cardiovascular disease, including various forms of cardiomyopathy [6] and are susceptible to SARS-CoV-2 infection [7].

By the end of 2020, various vaccines had been developed. However, they have certain limitations, particularly in the face of new variants of SARS-CoV-2. The continuous appearance of these variants, capable of evading immunity and/or with increased pathogenicity, represents a permanent threat to public health. Among them, the Alpha variant, one of the first to appear, and Omicron BQ.1, one of the most recent, have different virological and immunological profiles [8]. Patients infected with Omicron show an attenuated inflammatory response compared with those infected with Alpha, a difference attributed to specific mutations in several viral proteins [9].

Infection with SARS-CoV-2 causes major cellular perturbations, affecting mitochondria, the cytoskeleton, the endoplasmic reticulum and the Golgi apparatus [10]. The latter, a key structure in eukaryotic cells, takes the form of stacked membrane sacs and plays a central role in the post-translational modification, sorting and transport of proteins/lipids produced by the endoplasmic reticulum [11]. Recent studies have shown that the Golgi apparatus is directly involved in the SARS-CoV-2 viral cycle. The cellular stress generated by viral infection induces morphological alterations of the Golgi, notably its fragmentation, thus facilitating the assembly and secretion of new viral particles [12]. However, the underlying mechanisms and their pathophysiological implications are not clearly elucidated, and to date no comparative studies between the different variants have been carried out. A better understanding of these mechanisms could pave the way for new antiviral strategies based on disruption of viral particle assembly and secretion.

During the course of this thesis, the PhD candidate will seek to:

1) Generate cardiomyocytes (HiPSC-CM) from human induced pluripotent stem cells (HiPSC), select and characterize them (Z. Li Lab SU). Appropriate infection conditions will be set up for SARS-CoV-2 alpha and omicron BQ.1 variants (R. Suspène, Lab IP).

2) Determine, using photonic (confocal and super-resolution microscopy, Z. Li Lab SU) and electron (cryo-EM on Titan, R. Suspène, Lab IP) microscopy techniques, whether the alpha and/or BQ.1 variants induce morphological alterations of the Golgi apparatus in HiPSC-CM and whether these structural modifications are similar.

3) Identify the viral proteins involved in Golgi apparatus perturbations, as well as their cellular interactors. To this end, the candidate will use cell fractionation and Golgi apparatus enrichment techniques to study the impact of viral infections on the expression of a number of Golgi proteins (R. Suspène, Lab IP). In order to identify the viral proteins involved in these perturbations, co-immunoprecipitation and mass spectrometry experiments will be carried out (Z. Li Lab SU). The significant results thus obtained will be validated using CRISPR-Cas9 techniques for cellular proteins and viral clones lacking the viral proteins of interest (R. Suspène, Lab IP).

We hope to further our understanding of SARS-CoV-2-induced Golgi apparatus perturbations in cardiomyocytes and their role in cardiac injury.

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