SARS-COV-2: DIFFERENT AGE, DIFFERENT VIRION

Arturo Tozzi

Center for Nonlinear Science, Department of Physics, University of North Texas, Denton, Texas, USA
1155 Union Circle, #311427Denton, TX 76203-5017 USA
tozziarturo@libero.it
Arturo.Tozzi@unt.edu

Abstract

We suggest that the SARS-Cov-2 particles emerging from the cells of elder or pediatric hosts are phenotypically different, because they are equipped with a slightly different envelope. This might contribute to the well-documented variations of COVID-19 symptoms severity in populations of different ages.

One of the most intriguing questions raised during these frantic months of pandemics is: why are elder people more affected by SARS-Cov-2? Why do they suffer from severe COVID-19 symptoms, compared with the relatively spared pediatric population (see, e.g., Parri et al., 2020; Qiu et al., 2020)? Attempts at explanations are focusing on the role of ACE2 receptors (Bunyavanich et al., 2020), immunity (Wang et al., 2020), mandatory vaccinations (Tozzi 2020a), viral structural proteins, and so on. Nonetheless, an underrated virionic element could provide useful insights to tackle our crucial question. SARS-Cov-2 particles are made not just of RNA and the four main viral structural proteins - spike, membrane, envelope, and nucleocapsid proteins (Fehr and Perlman, 2016; Chen et al., 2020) -, but also of a "foreign" component, entirely provided by the host. The SARS-Cov-2 lipid wall is stolen from the human endoplasmic reticulum-Golgi intermediate compartment (ERGIC), i.e., the vesicular-tubular cluster which mediates trafficking between endoplasmic reticulum (ER) and Golgi complex (Appenzeller-Herzog and Hauri, 2006; Tozzi, 2020b) (**Figure, upper part**). It is no coincidence that coronaviruses display markers for the endoplasmic reticulum and Golgi (Brian and Baric, 2005). Like other enveloped viruses characterized by intracellular assembly, coronaviruses make use of the ERGIC membranes as a physical support for different steps of their vital cycle, such as replication and assembly by budding (Risco et al., 2002). Following replication and subgenomic RNA synthesis, viral structural proteins are translated (**Figure, upper part**). The ensuing proteins move along the secretory pathway and anchor to the physical support of the hosts' ERGIC membranes (Krijnse-Locker et al., 1994). After the assembly, the virions - including viral proteins, viral RNA and host ERGIC membranes - are transported to the cell surface in vesicles and released by exocytosis (Risco et al., 2002). In sum we may state that SARS-Cov-2 changes "skin" when jumping from a host to another.

ERGIC membranes and ageing. Once established that SARS-Cov-2 particles incorporate human ERGIC membranes, the next step it to examine whether such membranes are modified during senescence. Going through the literature, several clues point towards variations in human ERGIC membranes at different ages. It is well documented that biochemical, morphological and functional modifications of endoplasmic reticulum (REL) and Golgi membranes take place during ageing. From a long time ago, morphological studies in animals and humans revealed disorganization of the normally well-laminated pattern of REL and Golgi vescicles during senescence (Brizzee et al., 1975). Brouwer and Knook (1983) described the changes of cellular composition, morphology, function, physiology occurring in the reticuloendothelial system (RES) during aging. The interplay between RES and the immune system leads to increased susceptibility to infectious diseases and tumorogenesis during senescence. Back to the present, Desperes et al. (2019) identified ageing biomarkers associated with the Golgi apparatus. In contrast to the small and compact structure in non- senescent cells, the Golgi apparatus exhibited a large and expanded morphology in senescent fibroblasts. Further, the expression of numerous genes related to Golgi structural integrity and function was significantly altered. Cho et al. (2011) reported that the structure of the Golgi complex is dispersed in senescent cells. In particular, the upregulation of the G protein γ subunit γ11, which helps translocation from the plasma membrane to the Golgi complex, increases with ageing. Udono et al. (2015) showed that impaired expression of the senescence-associated gene ATP6V0A2 scatters the Golgi structure. Significantly different glycosylation structures in presenescent (young) and senescent (old) TIG-1 fibroblast cell lines were found.

Liu et al. (2018) described how the Serum Golgi protein 73 (GP73), a promising marker for liver fibrosis in adults, decreases with age in healthy controls. A hyperactive state of the protein secretory pathway mediates factors secretion and the fate of senescent cells. Su et al. (2018) investigated during cellular senescence the protein kinase D1 (PKD1)-mediated protein secretory pathway from the trans-Golgi network (TGN) to the cell surface. They found that components of this pathway, including PKD1, ADP-ribosylation factor 1 and phosphatidylinositol 4-kinase IIIβ, are increased at the TGN in senescent cells. The inhibition of this pathway reduces IL-6/IL-8 secretion during Ras oncogene-induced senescence (OIS), retards Ras OIS and alleviates the associated ER stress and autophagy. Janikiewicz et al. (2018)
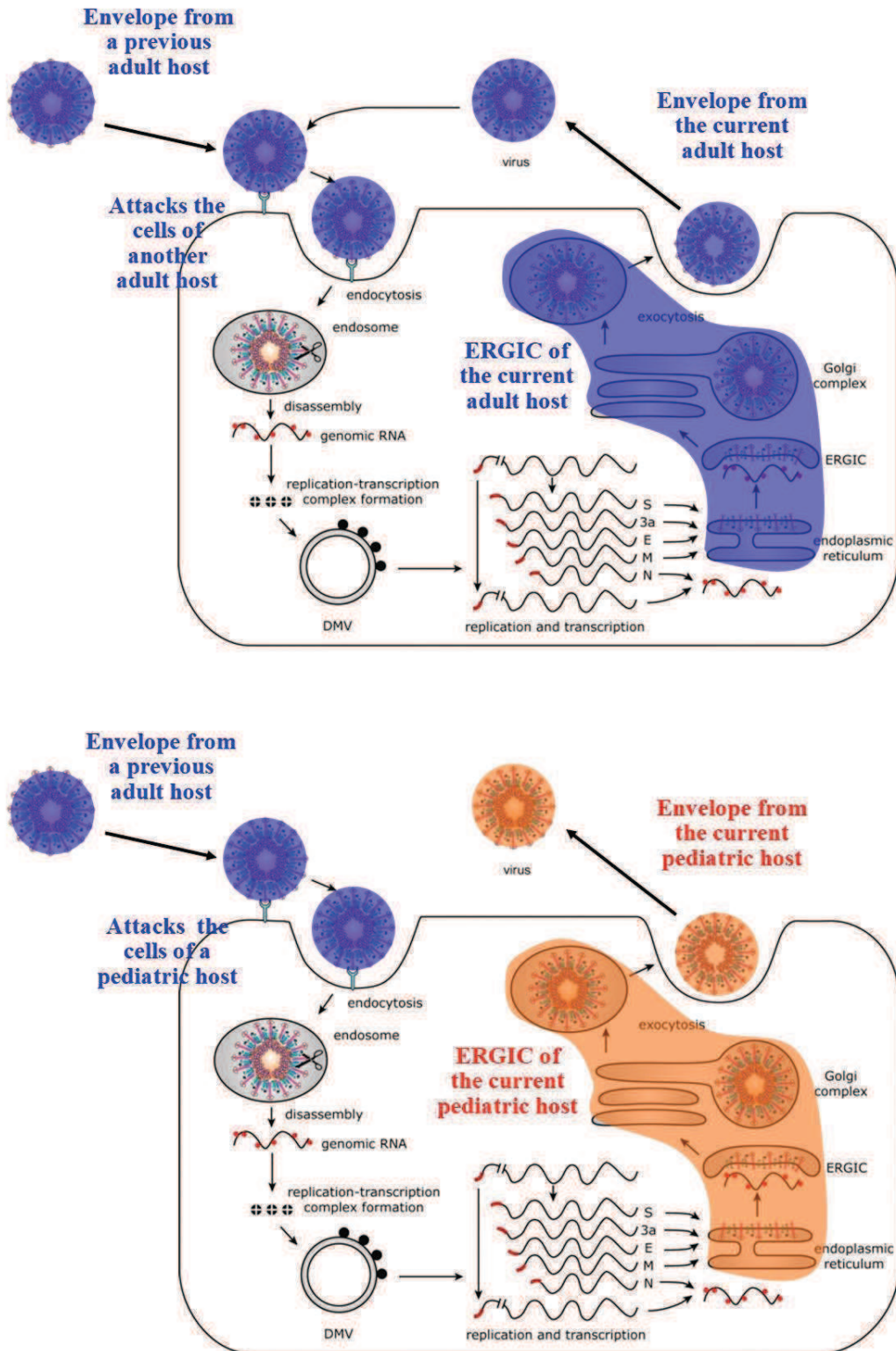
Figure. Replication pathway of SARS-Cov-2. Note that the ERGIC of the adult host's cell, depicted in blue (**upper figure**), is different from the ERGIC of the child host's cell, depicted in red (**lower figure**). This means that the virions released by old host cells (blue spheres) are phenotypically different from the virions released by young host cells (red pheres). Modified from: de Haan and Rottier (2006).

argued that mitochondrial and ER membranes' composition plays a role in longevity, via modifications in lipid biosynthesis and trafficking, calcium homeostasis, reactive oxygen species production and autophagy. Calvo-Rodríguez et al. (2016) suggested that neuronal aging is associated to increased ER-mitochondrial cross talking and subcellular Ca2+ remodeling. Acute murine γ-herpesvirus 68 infection, that causes apoptosis of type II lung epithelial cells in aging mice, up-regulates endoplasmic reticulum stress markers (Torres-González et al., 2012). Brown and Naidoo (2012) and Chadwick and Lajoie (2019) described the role of ER stress response pathways in aging and age-related diseases, occurring via pathways such as unfolded protein responses.

In sum, we may state that SARS-Cov-2 displays different "skins" when jumping from older to young hosts, and vice versa.

Phenotypical differences between SARS-Cov-2 emerging from young and old human cells. We can state that human ERGIC membranes change with time passing. This means that the SARS-Cov-2 particles produced in the tissues of children are phenotypically different from the SARS-Cov-2 particles produced in the tissues of elder people (**Figure, lower part**). Whether SARS-Cov-2 infects children, adults or elder people, the released virions will display different arrangement and composition of ERGIC membranes. We hypothesize that the virus particles emerging from the younger cells might be characterized by "favourable" features that either decrease particle stability and viral load, or reduce SARS-Cov-2 infectivity, or enhance host 's immunological responses. It has been observed that children are infected as adults, but do not display the more severe, life-threatening symptoms of COVID-19 seen in elder people. According to our framework, the explanation is straightforward: invasive SARS-Cov-2 particles emerged from an adult (say, a the severely-ill grandfather) are able to infect a child (say, his nephew); nevertheless, during the replication in the young tissues, the emerging SARS-Cov-2 novel particles become less dangerous and invasive, because they acquire the ERGIC membranes of the kid. If our hypothesis holds true, children are less infective than adults, even if their viral load might be the same as adults.

In sum, we may state that the different "skins" of SARS-Cov-2 lead to changes in COVID-19 severity.

ERGIC antibodies in COVID-19? We suggest to investigate the possible occurrence of Golgi and endoplasmic reticulum antibodies in the serum and bronchoalveolar liquid of patients affected by COVID-19. When intracellular structures like the Golgi complex and endoplasmic reticulum are extruded from a dying cell, their extracellular location may be the source of autoimmune reactions and production of specific monoclonal antibodies (Ma et al., 2019; Grossmann et al, 1989; Nozawa et al., 2002; Hong et al., 2004; Borradaile et al., 2006; Weber et al., 2010). This phenomenon, well described during cellular apoptosis and necrosis, might occur when new SARS-Cov-2 particles emerge in the respiratory airways from the infected cells too. The huge amount of ERGIC membranes' extracellular release during SARS-Cov-2 infection might be one of the factors that contribute to the lethal cytokine storm seen in COVID-19 (Fu et al., 2020). Antibodies against ER and ERGIC have been reported in human autoimmune diseases (Hong et al., 2004). For example, Bizzarro et al. (1999) detected anti-Golgi complex IgG antibodies in the sera of five patients during routine investigation for suspected systemic autoimmune disease. The phenomenon was transient in three patients with a probable viral infection, while it was persistent in the other two who developed an autoimmune disease a few years later. The anti-Golgi antibodies target the golgins, i.e., coiled-coil proteins anchored to the Golgi membrane that project into the surrounding cytoplasm (Witkos et al., 2015; Cheung and Pfeffer, 2016). This arrangement allows the tethering of nearby membranes or cytoskeletal elements (Satoh et al., 2019). The ability of golgins to aggregate different membranes might be responsible of the recently reported finding that SARS-COV-2 particles tend to aggregate and cluster together (Tozzi et al., 2020): in touch with this observation, it might be speculated that a different composition of golgins between children and elders might modify the ability of SARS-COV-2 to gather in larger structures that increase its fitness. The anti-Endoplasmic Reticulum antibodies target several resident proteins, e.g., calreticulin (Kotian et al., 2019). Calreticulin controls gene expression, calcium homeostasis regulation, molecular chaperoning and in particular, cellular adhesiveness: we speculate that this latter function might contribute to the different virulence of SARS-Cov-2 at distinct ages.

In sum, we may state that the different "skins" of SARS-Cov-2 produce different amounts of autoantibodies.

In conclusion, the different "skin features" of SARS-Cov-2 emerging from old and young cells might contribute to variations in clinical severity, viral load, infectivity.

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