

Review

# How physical factors coordinate virus infection – a perspective from mechanobiology

Wei Liu<sup>1,†</sup>, Daijiao Tang<sup>2,3,†</sup>, Xin-Xin Xu<sup>1</sup>, Yan-Jun Liu<sup>1,\*</sup> and Yaming Jiu<sup>2,3,\*</sup>

<sup>1</sup> Shanghai Institute of Cardiovascular Diseases, and the Shanghai Key Laboratory of Medical Epigenetics, the International Co-laboratory of Medical Epigenetics and Metabolism, Ministry of Science and Technology, Institutes of Biomedical Sciences, Zhongshan Hospital, Fudan University, Shanghai, 200032, China; 20111510004@fudan.edu.cn; 19111510004@fudan.edu.cn

<sup>2</sup> The Center for Microbes, Development and Health, Key Laboratory of Molecular Virology and Immunology, Institut Pasteur of Shanghai, Chinese Academy of Sciences, Shanghai 200031, China; djtang@ips.ac.cn

<sup>3</sup> University of Chinese Academy of Sciences, Yuquan Road No. 19(A), Shijingshan District, Beijing 100049, China;

\* Correspondence: ymjju@ips.ac.cn; Tel.: +86-21-54923175; Yanjun\_Liu@fudan.edu.cn; Tel.: +86-21-54237748

† These authors contributed equally to this manuscript.

**Abstract:** Pandemics caused by viruses have threatened lives of thousands of people. Viral infection is a complex and diverse process, and substantial studies have been complemented in understanding the biochemical and molecular interactions between viruses and hosts. However, the physical microenvironment where infections implement is often less carefully considered, and the role of mechanobiology in viral infection remains elusive. Mechanobiology focuses on sensation, transduction and response to intracellular and extracellular physical factors by tissues, cells and extracellular matrix. The intracellular cytoskeleton and mechanosensors have been proved to be extensively involved in virus life cycle. Furthermore, innovative methods *in vivo* and *in vitro* are being utilized to elucidate how extracellular factors including stiffness, forces and topography regulate viral infection. Our current review covers how physical factors from different sources coordinate virus infection. We further discuss how this knowledge can be harnessed in future research on cross-fields of mechanobiology and virology.

**Keywords:** virus infection; mechanobiology; cytoskeleton; mechanosensors; shear stress; tensile or compressive forces; topography; organ-on-a-chip

## 1. Introduction

Mechanobiology is a multidisciplinary research field ranging from biology to physics and it focuses on the circulation of mechanosensation, mechanotransduction and mechanoreponse [1,2]. With the in-depth research for complex mechanobiology, it has infiltrated including biology, physics, mathematics, engineering, medicine, as well as biotechnology and other areas [3–6]. Mechanical forces are ubiquitous exposure to cells, tissue, organs and individuals, which directly or indirectly regulate its function. At the cellular level, cytoskeleton including actin filaments, microtubules and intermedia filaments constitute dynamic cytoskeletal structures with varied binding proteins, which sense and transmit extracellular mechanical loads or generate mechanical cues to the surrounding extracellular matrix (ECM) (Figure 1 and Figure 2) [3]. Specifically, integrins as transmembrane mechanoreceptors sensed biomechanical changes and transmitted forces to the cytoskeleton [7]. During morphogenesis, biochemical factors like morphogens coupling with intrinsic and extrinsic mechanical cues were of vital importance in driving embryogenesis [2,8]. *In vivo*, cell behaviors are precisely regulated by multiple factors including cell types, cell states, secretory proteins and environmental information in the niche. In the microenvironments, there are various physical elements such as fluids, confined space and topography apart from biological and chemical context of cells.

These forces individually or together exert mechanical cues to regulate cell behaviors (Figure 2a). Consequently, it is essential to develop advanced techniques to disentangle these physical elements and study how individual mechanical cue affects cell behaviors. Attributing to the pioneering technologies, systems applied in mechanobiology have increasingly developed at a very fast pace and provide significant insights into mechanobiology.

Mechanobiology as an emerging research discipline has already extended to virology. Extrinsic and intrinsic mechanical forces can promote or impact virus infection. In this review, we focus on how to decouple each mechanical force *in vivo* and mimic the physical microenvironments *in vitro*, and elaborate how mechanical forces influence the process of viral invasion.

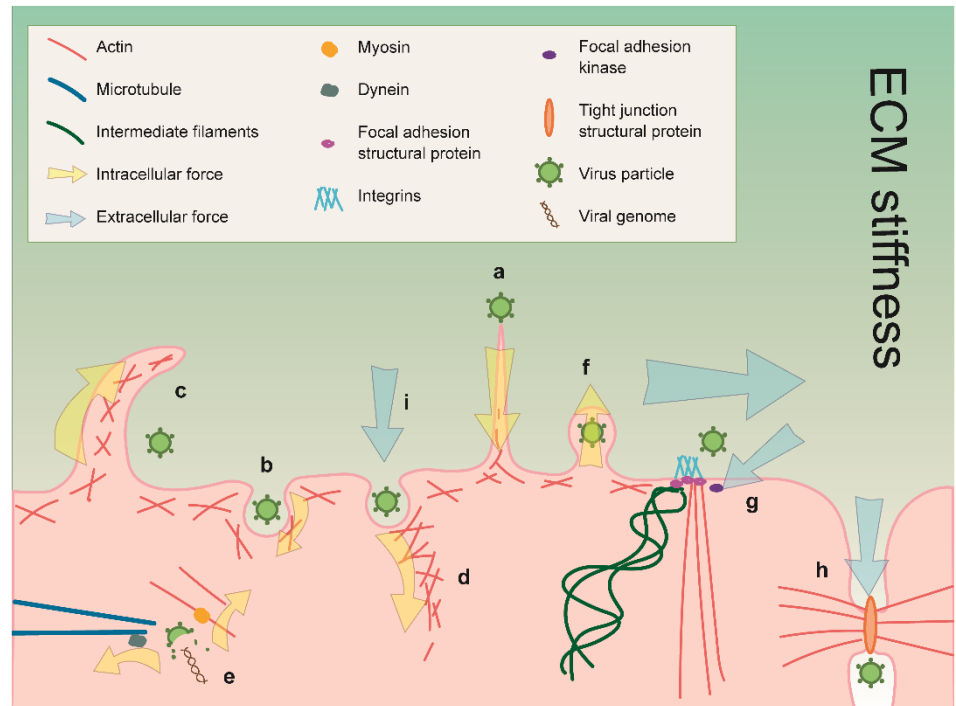
## 2. Numerous physical parameters affect virus infection

In cells, cytoskeleton is the structure that most intimately associated with cell mechanics. It functions in a lot of cell activities including cell motility, cell morphology, intracellular transportation, cell division, force transmission, endocytosis, etc. There are three types of cytoskeletons: microtubules, actin filaments and intermediate filaments (Figure 1) [9]. Microtubules and actin filaments potentially provide forces for every steps of virus life cycle, from entry to uncoating, from assembly to egress. Microtubule motors kinesin, dynein and their accessories such as dynactin complex are responsible for force generation to drive cell activities like intracellular transportation and endocytosis [10]. Actin motors myosin and actin polymerization factors like Arp2/3 complex are critical for force generation by actin filaments [11]. Intermediate filaments can be divided into six types, each is formed by different kinds of proteins. Intermediate filaments are significant for cells to resist stress and, together with microtubules and actin filaments, could sense extracellular mechanical signals by associating with mechanosensors and activate downstream signaling pathways [12,13]. Many viral infections are dependent on mechanosensors and their protein components, thus providing another way for cytoskeleton to mechanically regulate viral infections [14].

Extracellular mechanical signals are transmitted into cells by different mechanosensors and lead to a series of cell mechanics changes. In next section, we will focus on three kinds of mechanosensors: focal adhesion, cell-cell junction and caveolae, to introduce their roles during viral infection (Figure 1). Focal adhesion is large adhesion contacts at the ends of actin stress fibers [15]. Its structure protein integrin and regulatory protein focal adhesion kinase (FAK) are able to sense mechanical signals including tensile forces, shear stress, extracellular matrix stiffness, etc. Meanwhile, focal adhesion is employed by a lot of viruses to facilitate their infection. Cell-cell junctions link cells to each other in tissues. There are three types of cell-cell junctions, including tight junctions, adherent junctions and desmosomes [16]. Cell-cell junctions can sense forces from intracellular and extracellular environment and transduce the mechanical signals to promote cell adaptations to the environment [17]. Cell-cell junctions are also involved in viral infections, and affect viral infections in various ways. Caveolae are rounded invaginations on plasma membrane, and caveolin-1 and cavin-1 are indispensable structural proteins of it. Extracellular stress is proved to be sensed by caveolae and could alter its number, morphology and localization [18]. Since many viral infections are dependent on caveolae [19], caveolae may bridge the interactions between viral infections and stress.

Extracellular mechanical forces during virus infection are divided into four types: shear stress, tensile or compressive forces, 3D ECM and topography of substrates (Figure 2a). *In vivo*, bloodstream flowing above epithelial cells generates shear stress on cells and alter their formation and function [20]. Extracellular shear stress has been confirmed to influence viral infections in different *in vitro* models. Tensile or compressive forces, sensed by cytoskeleton and mechanosensors, may affect viral infection at multiple aspects. Organ-on-a-chip models have been employed to study the viral infections in the presence of mechanical forces [21]. Tissue stiffness could be changed by noninfectious

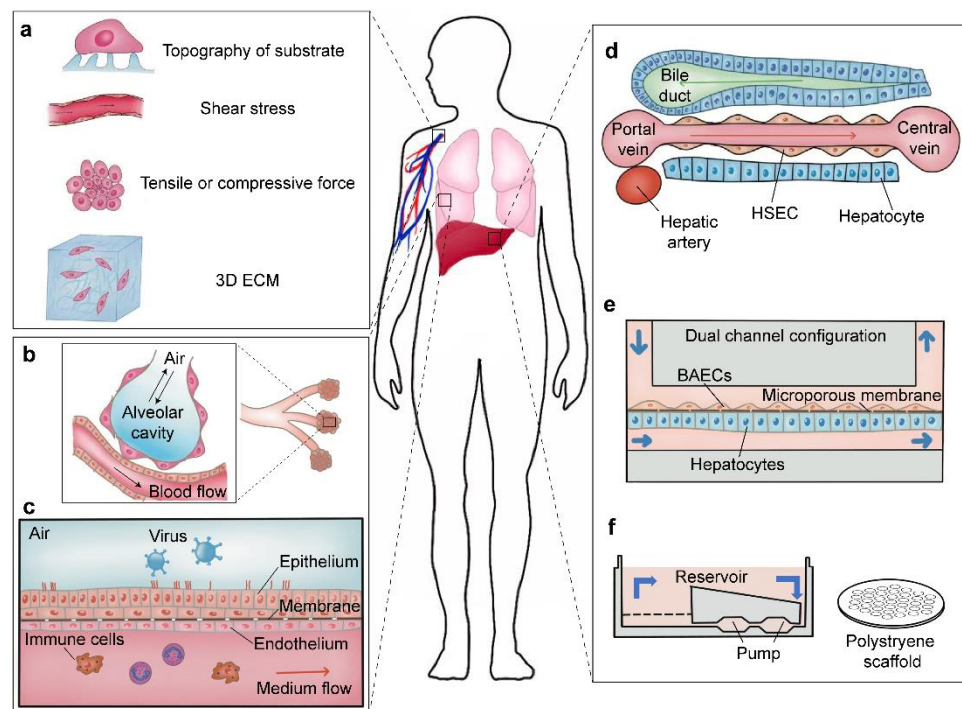
[22] and infectious factors such as viral infection [23]. It could be sensed by focal adhesions and results in extensive cell mechanical changes, which might affect different steps in viral infections. Different tissues have various topography, which may influence cell mechanics and motility, thus affect viral infection and transmission [24].



**Figure 1.** Cytoskeleton and mechanosensors play crucial roles during viral infections. (a) Actin filaments in host cells participate in virus surfing before entering into the cells. (b) Actin filaments provide forces for virus entry through clathrin-mediated endocytosis. (c) Macropinocytosis is employed by viruses for entry which is an actin-dependent process. (d) Actin monomers undergo rapid polymerization to generate forces for viral entry through caveolae-mediated endocytosis. (e) Microtubule and actin filaments motor proteins dynein and myosin may provide forces for virus uncoating, respectively. (f) Actin filaments provide bending force to expel viruses to the extracellular environment. (g) Focal adhesion and FAK can sense extracellular mechanical signals such as shear force (horizontal arrow), tensile forces (slanting arrow) and ECM stiffness (gradient background color). Focal adhesion proteins can also affect viral infection in multiple ways. (h) Cell-cell junctions sense forces from intracellular and extracellular environment, and may be employed by viruses to facilitate their infection. (i) Caveolae sense extracellular stress. The number, morphology and localization of caveolae are altered in response to stress and further affect viral infection.

### 3. Host cytoskeleton and mechanosensors during viral infection

Cytoskeleton and mechanosensors are significant intracellular physical factors that may alter cell mechanics and influence viral infections (Figure 1). Cytoskeleton is responsible for generating forces for various cell activities. During viral infection, the forces generated by cytoskeleton might be utilized by viruses to facilitate their infections. Cytoskeleton can also sense mechanical cues by associating with mechanosensors [13]. Mechanosensors are cell structures and proteins that are able to sense different kinds of extracellular mechanical signals and transduce them to intracellular to activate downstream signaling pathways and lead to cell mechanic changes. These changes may affect viral infections indirectly in multiple ways. Besides, mechanosensors might be employed by viruses to facilitate their infection. Therefore, how mechanosensors regulate viral infection mechanically may be a potential research field and lead to discovery of new antiviral targets.



**Figure 2.** Extracellular mechanical forces *in vivo* and organ-on-a-chip models for virology *in vitro*. (a) Extracellular mechanical forces existing in human body. Extrinsic physical parameters are ubiquitous *in vivo* like topography of substrate formed by ECM, shear stress from fluid flow, tensile or compressive forces and 3D ECM. (b) Physiological microenvironment in human pulmonary alveoli. Shear force generated by blood flow and tensile force exerted on alveolar cavity are important mechanical parameters for respiratory virus infection. (c) Schematic diagram of lung-on-a-chip (adapted from Longlong Si et al. [25]). This biochip reconstituted alveolar microenvironment including simulating blood flow and air exchange. (d) Physiological microenvironment in human liver sinusoid. Shear stress derived from biological flow is a crucial factor for maintaining the differentiation of hepatocytes *in vitro*. (e) Schematic diagram of a dual channel microdevice mimicking hepatic sinusoid (adapted from Young Bok (Abraham) Kang et al. [26]). (f) Schematic of another liver-on-a-chip (adapted from A.M. Ortega-Prieto et al. [27]).

### 3.1. How Cytoskeleton Mechanically Regulates Viral Infection

Actin cytoskeleton and microtubules, with their associated proteins, are able to respond to a variety of mechanical signals and generate physical forces for plenty of cell activities, such as intracellular cargo transportation and cell motility [13]. Intermediate filaments are well known to provide mechanical support against stress [12]. Importantly, cytoskeleton is extensively involved in viral infection, functioning as transporters of viral particles, physical barriers to resist virus entry, etc [12]. Therefore, the mechanical properties of cytoskeleton should be a significant factor required to be considered in virology studies. In this part, we summarize recent studies about how host cytoskeleton affects viral infection through mechanical regulation and advanced insights of this research field.

After binding to certain receptors on the plasma membrane, it is necessary for viruses to migrate to preferred sites for entry. The most common form of this process is virus surfing, an actin-dependent movement of virus towards cell body. The underlying mechanism revealed that actomyosin generates forces for retrograde flow and subsequently pulls the filopodia-associated actin filaments towards the cell body [28]. It had been proved that the entry of murine leukemia virus (MLV) [29] and herpes simplex virus (HSV) utilized virus surfing in an actin-dependent manner [30].

The majority of viruses enter cells through endocytosis [31,32], which is further divided into clathrin-mediated endocytosis and caveolae-mediated endocytosis. Actin cy-

toskeleton and microtubules are indispensable for endocytosis due to their force-generating ability. Arp2/3 complex, myosin and other actin related proteins together control and regulate the polymerization and growth of actin network, and provide force to generate the invagination of membrane in clathrin-mediated endocytosis [33]. Rhabdoviruses entered cells through clathrin-mediated pathway in an actin-dependent manner: cytochalasin D treatment impeded viral entry [34]. Adenoviruses entry was through clathrin-mediated, actin and dynein dependent endocytosis [35]. Mosquito-borne flaviviruses, such as Japanese encephalitis virus (JEV) and West Nile virus (WNV), typically entered cells through clathrin-mediated pathway. The disruption of actin filaments using cytochalasin D and jasplakinolide inhibited JEV entry [36] and the disruption of the microtubule network by nocodazole strongly affected WNV entry [37]. Actin dynamics are also necessary for Kaposi's sarcoma-associated herpesvirus (KSHV) entry through clathrin-mediated endocytosis since disruption of the actin cytoskeleton and inhibition of regulators of actin nucleation blocked KSHV entry and trafficking [38].

Macropinocytosis is even more tightly associated with actin, since it's an actin-driven process. Actin polymerizes in a ring under the cell membrane to form the macropinocytic cup, and myosin provides contractile force for the cup to close and seal [39]. KSHV entered human dermal microvascular endothelial (HMVEC-d) cells predominantly through macropinocytosis, and the infection induced myosin light chain II phosphorylation. Myosin might provide forces to produce the movement requested by the process of bleb retraction [40]. Knockdown of TSPAN7, a regulator of actin nucleation, led to increased macropinocytosis of human immunodeficiency virus-1 (HIV-1) in dendritic cells, while inhibition of actomyosin contraction was able to rescue the knock-down [41]. Hantaan virus (HTNV) and Andes orthohantavirus (ANDV) entered human respiratory epithelial cells probably through macropinocytosis since their entry depended on sodium proton exchangers and actin [42].

Actin polymerization is also essential for the formation and budding of caveolae [43]. Simian virus 40 (SV40) is well-known for employing caveolae-mediated endocytosis pathway for entry. Specifically, SV40 triggered a signal transduction cascade which led to depolymerization of the actin filaments under plasma membranes. Generated actin monomers were then recruited to the virus-loaded caveolae and formed actin patch, on which a burst of actin polymerization occurred. Virus-loaded caveolae vesicles were subsequently released from the membrane and moved into the cytoplasm [44]. Before transmissible gastroenteritis virus (TGEV) internalization, caveolin-1 would gather around the viruses with the assistance of actin and clathrin to form the vesicle containing TGEV, and after ~60 seconds, dynamin 2 were recruited to promote membrane fission [45].

Apart from endocytosis, cytoskeleton network also functions in uncoating, replication and assembly steps during virus life cycle. Microtubule- and actin-associated motors, including dynactin, dynein and myosin II, generated physical forces to help to break apart capsids of influenza A virus (IAV) and thus promoted its entry [46]. Cytoskeleton rearrangement and dynamic changes are common phenomena among a lot of viruses' replications, such as coronavirus [47] and HIV-1 [48] and may mechanically affect viral replication, since cytoskeleton rearrangements always lead to extensive cell mechanic changes [28]. Cytoplasmic forces also contributed to vaccinia viral replication by translocating the replication sites towards nucleus [49]. As for assembly, it was theoretically assumed that actin filaments provide protrusive forces to initiate assembly during retroviral infection [50].

In addition, cytoskeleton is indispensable for the egress of viruses. Actin nucleation might offer driving force to expel virus from membrane pits to extracellular environment [51]. Release of vaccinia virus (VACV) required the force of actin nucleation to reduce association between extracellular virus and plasma membrane [52]. During measles virus (MV) budding, actin cytoskeleton performed a vectorial growth which might generate forces contributing to the formation of viral buds [53]. Intact actin cytoskeleton was crucial in providing force necessary to expel WNV to extracellular environment [54]. In

SARS coronavirus infected cells, actin filaments which were parallel to the cell edge might thicken to provide bending force to expel viral particles from the plasma membrane [55].

In addition to affecting different steps in virus life cycle, actin cytoskeleton regulates viral infection by altering signaling pathways. Rho-ROCK-Myosin II contractility signaling pathway increased cell stiffness and formed a physical barrier against viral infection [56]. Decreased actin polymerization led to the translocation of NF- $\kappa$ B transcription factor p65 to the nucleus, and NF- $\kappa$ B signaling pathway was known to have antiviral function [57]. Cytoskeleton is so closely related to cell mechanics that can alter a great amount of cell activities and affect viral infection indirectly.

Different types of intermediate filaments locate at different sites and execute distinguish functions. Although they don't have motor proteins like actin filaments and microtubules do, they are indispensable for cells to resist stress and are involved in the mechanosensing of cells. Therefore, they are vital for a variety of cell activities including cell migration, mitosis, cell growth and stress-mediated responses [58]. Keratin adapts to different matrix rigidities, regulates stiffness-dependent F-actin remodeling and transduces the mechanical signals to nucleus lamina [59]. Focal adhesion-anchored vimentin could regulate mechanosensing by activating FAK and its downstream signaling pathways [14]. Intermediate filaments also affect viral infection in multiple aspects. Cell surface vimentin functioned as co-receptor to help SARS-CoV spike protein bind to receptor angiotensin-converting enzyme 2 (ACE2) [60]. For human papillomavirus 16 pseudovirions (HPV16-PsVs), knocking down of cell surface vimentin with siRNA significantly increased its binding and internalization [61]. Vimentin was also critical for IAV genome penetration into the cytoplasm to facilitate viral infection. Vimentin depletion severely reduced IAV RNA, protein expression and production of infectious viral particles [62].

### 3.2. Mechanosensors

Numerous cell structures and molecules are able to sense and respond to extracellular mechanical signals. Among them, focal adhesion, cell-cell junction and caveolae are extensively studied and intimately associated with viral infection (Figure 1), although few studies have explored the relationship between these mechanosensors and viral infection from the perspective of mechanobiology. We summarize how these mechanosensors sense mechanical cues and affect diverse steps directly or indirectly during viral infection.

Focal adhesion is a specialized region on the plasma membrane at which actin bundles are anchored to the integrin transmembrane receptors through a multi-molecular complex of junctional plaque proteins [15]. Integrin interacts with extracellular matrix proteins to sense shear stress and activates downstream signaling molecules in focal adhesions and cytoplasm [63]. FAK is a well-known mechanosensor which is activated by tensile forces transmitted from cytoskeleton-anchored focal adhesion targeting (FAT) domain and membrane through phosphoinositide phosphatidylinositol-4,5-bis-phosphate (PtdIns(4,5)P<sub>2</sub>) binding site [64]. Focal adhesion and related proteins are also involved in viral infection in numerous aspects. For instance, FAK regulates the phosphorylation and transcriptional activity of NF- $\kappa$ B in response to fluid shear stress [65]. Porcine hemagglutinating encephalomyelitis virus (PHEV) caused an actin filaments rearrangement through integrin  $\alpha$ 5 $\beta$ 1-FAK-Rac1/Cdc42-PAK-LIMK-cofilin pathway to facilitate its own infection [66]. IAV hijacked FAK to promote its replication and inhibited FAK from activating innate immune responses [67]. Integrin was employed by a variety of viruses as cellular receptor or internalization factor, such as WNV [68], zika virus (ZIKV) [69], adeno-associated virus (AAV) [70] and adenovirus [71], to promote their infection.

Cell-cell junctions connect cells with each other and regulate tissue homeostasis during tissue barrier homeostasis, cell proliferation and migration. They also function in mechanosensing and mechanotransduction of forces from multiple sources, such as ex-

ternal forces applied at the tissue scale, forces generated within tissues and cellular contractility [17]. Tight junction, a type of cell-cell junction, usually serves as physical barriers to resist pathogens invasion. However, some viruses may interact with tight junction related proteins to promote their entry. The best-studied case is that adenovirus bound to coxsackievirus and adenovirus receptor (CAR), a tight junction integral protein to cross human airway epithelial layer and entered cells for replication [72]. Claudin-1, another tight junction protein, was an hepatitis C virus (HCV) co-receptor required for its entry [73]. In addition to tight junction associated proteins, adherent junction protein nectin-4 served as epithelial receptor for MV [74].

Caveolae have been confirmed to undergo assembly and disassembly as well as localization and morphology change in response to mechanical stress [18,75]. Caveolin-1 (Cav-1), a critical protein component of caveolae, is significant in regulating actin-related mechanosensitive pathways [76]. Meanwhile, caveolae not only regulates viral entry but also other steps in viral life cycle. Cav-1 bound to HIV Env protein at caveolae lipid raft, and the interaction blocked HIV fusion and reduced virus replication [77]. Respiratory syncytial virus (RSV) morphogenesis proceeded within caveolae, and both Cav-1 and cavin-1, two major components of caveolae, were recruited to and incorporated into the RSV envelope, which occurred just before RSV filament assembly [78]. Paramyxovirus parainfluenza virus 5 (PIV-5) virions lacking Cav-1 were defective and contained high levels of host proteins and low levels of viral hemagglutinin-neuraminidase (HN) and matrix (M) proteins, suggesting that Cav-1 was incorporated in mature PIV-5 particles. Besides, Cav-1 was clustered at sites of PIV-5 budding [79]. Human parainfluenza virus type 2 (hPIV-2) V protein bound to and stabilized cavin-3, which in turn promoted assembly and budding of hPIV-2 in lipid raft microdomains [80].

#### 4. Extracellular mechanical forces during virus infection

There are various culture systems *in vitro* that have been applied in virology, aiming at elucidating the pathogenesis of virus infection, host-virus interactions and host immune responses, and dedicating to drug discovery and vaccine development. Most of these culture systems are built on 2D multi-wells plates in which cells are seeded on plastic or glass bottom during virus infection. However, it is much more sophisticated pathophysiology for host-virus interactions *in vivo* [8]. For example, vascular endothelial cells are exposed to shear forces of bloodstream rather than in static culture condition. One of the disadvantages of conventional models of virus infection is that these systems can not accurately simulate the real microenvironment of viral infection. Micro- and nano-fabrication technology have been rapidly evolved in recent years and established novel approaches to study how mechanical forces influence virus infection *in vitro*, which can better mimic the microenvironment *in vivo* [81]. Here, important extrinsic mechanical forces *in vivo* during virus infection are divided into three types: shear stress, tensile or compressive forces and topography of substrate (Figure 2a). We summarize the extrinsic mechanical forces that affect kinetics and pathogenesis of viral infection and discuss how these physical factors can be applied in the future antiviral studies.

##### 4.1. Shear Stress

Shear stress, a frictional force generated by blood stream, exerts mechanical stimulus on endothelial cells that affect its function [20,82]. During early embryo development, it is vital for fluid shear stress to adjust and control left-right body asymmetry [8]. Under realistic physiological conditions, biological fluids serve as naturally physical barriers to hold back adsorption and invasion of the causative agent and therefore pathogens have developed exquisite strategies to break through physical shear forces in the body [83].

Shear-flow turbulence at some specific sites in blood vessels can function as mechanical cues to activate latently herpes virus-infected endothelial cells [84]. This kind of activation changed expression of heparans on cell surface, which was one of the causative factors inducing atherogenesis. Similarly, exposure to low shear stress which mimicked

mechanical microenvironment of atheroprone regions *in vivo* promoted the infection of human cytomegalovirus (HCMV) to endothelial cells [85]. However, there were little significant differences for HCMV infection when endothelial cells were under high shear stress or in static conditions. Shear forces applied to endothelial cells would alter the gene expression. Comparing brain endothelial cells cultivated in conventional 2D and 3D printed vascular model, shear-flow in 3D model increased the expression of angiotensin-converting enzyme-2 (ACE2) resulting in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [86]. Dynamic culture system in microchannel provided NIH/3T3 cells with more susceptible condition for virus infection in contrast with conventional petri dish culture [87]. These studies demonstrated that shear forces from blood flow is a crucial mechanical stimulus affecting virus infection. *In vitro*, propagation and production of virus models also confirmed that the flowing shear stress influenced virus infection. A suitable shear stress below  $0.25 \text{ N m}^{-2}$  would enhance the titers of oncolytic measles virus in the viral propagation model [88]. Hydrodynamic shear forces generated from agitated bioreactor increased propagation of JEV in Vero cells [89]. Notably, the value of shear stress can be different in different culture systems as agitator-dependent shear over  $0.25 \text{ N m}^{-2}$  would decrease the titer of oncolytic measles virus [88], and shear stress origin from gas bubbles was harmful for baculovirus expressed vector system [90]. It was proposed that increased endothelial pulsatile shear stress can be a good choice to prevent SARS-CoV-2 infection by increasing bioavailability of nitric oxide (NO) [91]. Different classes of cells exposed to the same value of shear forces also showed different performances during viral infection. Compared with BHK-21 cells, Vero cells in microcarrier were more vulnerable to JEV [89]. Viral invasion can cause cytopathogenic effect (CPE) in individual cell. Interestingly, vaccinia virus, a member of poxvirus, promoted cell migration which was one of distinctive CPE [92]. It was also found that there is enhanced directional cell migration induced by VACV in the presence of shear stress in microfluidic device [93]. That was because that the fluid flow reduced extra lamellipodium around infected cell and changed the orientation of Golgi complex.

What's more, emergence of human organ-on-a-chip offers new insights to investigate the mechanisms of virus-host interactions [81]. To improve conventional viral models and better simulate real microenvironment *in vivo*, shear stress as a significant mechanical cue is usually introduced into organ-on-a-chip (Figure 2c, 2e and 2f). It was proved that the recirculation of culture media was helpful to recapitulate the complex hepatic sinusoid *in vitro* and this 3D microfluidic model can be applied to study the dynamics and mechanism of hepatitis B virus (HBV) infection [27]. Shear forces also applied to the distal renal tubules model to explore the association between renal dysfunctions and virus infection [94].

#### 4.2. Tensile or Compressive Forces

External forces like tensile or compressive forces play a significant role in tissue morphogenesis. Mitotic spindle orientation can be modulated by applied stretch forces, which was associated with the location of cortical actin [95]. During metastasis events, the tumor cells adjusted themselves to mechanical cues (such as ECM stiffness, compressive stress and shear stress) of microenvironment for their survival [96]. Importantly, this type of force also affects viral infection from multiple aspects. Enteroviruses, a type of non-enveloped, single-stranded RNA viruses, primarily infect gastrointestinal epithelial cells, contributing to the occurrence of many diseases including exanthemas and poliomyelitis [97]. Due to the complicated microstructure of human intestinal epithelium, it is too simplified to use monolayer cells *in vitro* as infection model to study enteric virus biology. Cyclic suction designed for exerting tension and compression force was used in human gut-on-a-chip in order to mimic gastrointestinal peristalsis [21]. This device displayed excellent performance for villus-like structure formation and coxsackievirus B1 (CVB1) infection. The model showed that virus particles and inflammatory cytokines

were detected at the cell apex, indicating that the mechanical forces were essential elements of the recapitulating complex intestinal epithelial microenvironment.

#### 4.3. Topography of Substrate

Micro/nanostructured topographies of ECM pose a great diversity of mechanical cues to the cells or tissues surrounding them. Contact guidance as a way of cell-responses to topographies is a general phenomenon during cell migration *in vivo* [98]. Fibroblasts exhibited different forms of morphologies in responding to different topographies of substrate [99]. Topography also influences virus infection and transmission. Vero cells seeded on microgrooved substrate showed anisotropic cell-to-cell transmission of VACV compared with smooth substrate [24]. Cytoskeleton rearrangement played a major role in cellular response to microgrooved substrate that accounted for this re-direction of cell-to-cell viral spread. As mentioned above, VACV infection promotes epithelial cells migration to speed up the spread of the virus. Topographic microstructures acting as contact guidance facilitated directed cell motility induced by VACV [100]. Reorientation of the Golgi complex and a dominant elongated protrusion was responsible for this directed cell migration.

#### 4.4. Organ-on-a-Chip

Although different mechanical parameters have been individually investigated during viral infection, it is not sufficient to thoroughly understand the interplay between dynamic physiochemical microenvironments and infectious viral particles. Advent of organ-on-a-chip technologies provides novel insights to explore how spatial information regulate virus infection, which recapitulate the sophisticated microarchitecture of localized tissue and dynamic physiochemical microenvironments.

Advanced lung chip mimicking alveolar-capillary interface of the human body (Figure 2b) reconstituted an ingenious microdevice to offer alternative model for drug discovery and preclinical trial [101]. Mechanical cues like shear stress, tensile or compressive forces and 3D co-culture were integrated in this microsystem to achieve organ-level lung chip. Using this lung chip, more detailed information and new phenomena during influenza virus and SARS-CoV-2 infection can be achievable, and cytokine M-CSF may be identified as candidate maker indicating chronic obstructive pulmonary disease (COPD) caused by respiratory viruses [102,103]. In another lung chip, NCI-H441 cells and human bronchial epithelial cells were co-cultured with monocyte-derived macrophages on the interface of a porous membrane that further resembled cellular component of human alveolus [104]. Shear forces created by peristaltic pumps and co-culture of circulating immune cells increased barrier integrity formed in this biochip [105]. Co-infection of influenza virus and staphylococcus aureus destroyed the vascular endothelial barrier rather than alveolar epithelial barrier, showing that pathogens infection can cause multi-impacts on the alveoli of the lungs. The same type of biochip was constructed to identify key features of human rhinovirus strain 16 (HRV-16) induced exacerbation of asthma [106].

The hepatic sinusoid universally found in liver is a kind of special capillary, which is regarded as functional unit of liver activity (Figure 2d). A liver sinusoid provides a venue for mixing oxygen-rich arterial blood and nutrient-rich venous blood, and also serves as portal of entry for hepatitis virus [107]. To date, few models *in vitro* mimicking the hepatic sinusoid are available, due to the complex components of sinusoid and de-differentiation of primary human hepatocyte cultured *in vitro* [108–110]. Liver-on-a-chip can offer a feasible solution. A dual-channel chip was separated by a porous membrane simulating the space of Disse between sinusoidal endothelial cells and hepatocytes. Primary rat hepatocytes or primary human hepatocytes and immortalized bovine aortic endothelial cells were cultivated on the opposite surface of the membrane with continuous perfusion device mimicking shear stress from fluid flow (Figure 2e) [26,111]. Under the condition of combined mechanical forces, primary hepatocytes in the

chip can maintain their polygonal morphology more than three weeks. Recombinant adenoviruses encoding genome of HBV or isolated HBV from HepG2.215 or HepAD38 cell-culture was able to infect hepatocytes in microchannel and accomplish HBV replication that verified the practicability of this kind of liver chip. Furthermore, a more simplified 3D microfluidic liver chip was developed to study HBV and screening of new anti-HBV drugs. This configuration with the recirculation of culture media used collagen-coated polystyrene scaffold as substrate supporting primary human hepatocytes (Figure 2f) [27,112]. This platform only containing scaffold and circulatory system was much simpler compared with the microsystems described above. Primary human hepatocyte alone or co-cultured with primary Kupffer cells retained viability and dedifferentiated phenotype in this device for up to 40 days. Not only HepDE19-derived HBV at a low MOI=0.05 genome equivalents (GE) /cell were able to infect 3D hepatocytes, but also patient-derived HBV at a high MOI=100 GE/cell. The secretion of cytokines (IL-8, macrophage-inflammatory protein (MIP)-3 $\alpha$ , SerpinE1, and monocyte chemoattractant protein-1 (MCP-1)) was similar to the test results from the sera of HBV-infected patients. This 3D microfluidic liver chip showed great potential in the application of anti-HBV therapy.

Gastrointestinal mucosae initially interact with enterovirus and are considered as an ideal architecture exploring host-pathogen interplay. These tissues are constituted by multi-complex elements such as numerous cell types, 3D tissue architecture and intestinal gurgling [113]. However, enterovirus models *in vitro* mostly build on single type cell culture forming flat monolayers, which lacks precise regulation of the dynamic microenvironments. A human gut-on-a-chip explored how dynamic mechanical forces influenced intestinal function [114]. This micro-engineered device comprised of three parallel microchannels fabricated by poly(dimethylsiloxane) (PDMS). The central channel was separated by ECM-coated PDMS membrane and the two-sided channels were drove by cyclic suction to generate cyclic peristalsis-like mechanical deformations. When ceasing tensile and compressive forces that exerted on human intestinal epithelial cells by stopping cyclic suction and remaining fluidic flow, the growth of enteric microorganism was promoted, which meant mechanical cues influenced interactions of host and pathogen. This micro-engineered model was further improved to apply in CVB1 infected model [21]. Caco-2 intestinal epithelial cells cultured in this gut-on-a-chip displayed villus-like structures under conditions of continuous perfusion and cyclic mechanical strain. In this chip, viral particles and cytokines induced by CVB1 tended to be released from the apex, implying the polarized infection of CVB1 in gastrointestinal microenvironments.

Similar construction utilizing porous membrane played a role in kidney-on-a-chip to study virus-related renal dysfunctions [94]. Madin-Darby Canine Kidney (MDCK) cells were cultured on the upper surface of porous membrane and exposed to microfluidic flow mimicking shear force from tubular flow distal renal tubules. Distal tubule-on-a-chip (DTC) combining shear stress with confined force provided epithelial cells a suitable physical microenvironment to form self-assembled microvilli. During pseudorabies virus infection, the disordered function of Na<sup>+</sup> reabsorption and intertwined microvilli in DTC were observed, which opened new perspectives of dynamic changes after virus infection. Recently, Ebola virus model built on microvessel-on-a-chip permitted mechanistic studies of Ebola hemorrhagic syndrome. The study showed that Ebola glycoprotein (GP1,2) hijacked Rho/ROCK pathway and modulated host cytoskeleton resulting in albumin leakage from the biomimetic vascular wall [115]. It was worth noting that Ebola VLPs did not contain viral genome and this phenotype was induced only by the glycoprotein on the surface of the virus.

## 5. Conclusions and perspectives

### 5.1. Mechanosensors

Mechanosensors mentioned above are cellular elements that compose of diverse proteins. However, many other mechanosensors are proteins that function individually to sense mechanical signals. For example, Notch-1 is able to response to shear stress, and

is necessary for the maintenance of many cell structures and activities such as junction integrity, cell elongation and proliferation [116]. These mechanosensors are also involved in viral infection. The N-terminal portion of Notch-1 interacted specifically with p50 subunit and inhibited p50 DNA binding of NF- $\kappa$ B [117]. Nevertheless, like mechanosensors discussed above, few of their effects on viral infections are studied from a mechanobiological perspective, which might be a potential study direction. One example is that Yes-Associated Protein (YAP) could suppress T cell proliferation in a stiffness dependent manner and regulate T cell responses against viral infection [118]. YAP functions as mechanosensor bridging cell mechanics and viral infection. Studies focusing on mechanosensors and viral infections may elucidate how cell and tissue mechanics regulate viral life cycle and potentially provide new antiviral targets. It is also possible to link some diseases that are closely associated with tissue mechanical changes, for example, hypertension, with viral infection, which may be able to explain why some virus infection can cause these diseases [119], and why people who suffered from these diseases have higher susceptibilities to certain viruses compared with healthy people [120].

### 5.2. Infection-caused Cell Mechanical Changes

Viral infection can not only be regulated by cell mechanics, but also cause changes of cell mechanics. A common infection-caused cell mechanical change is cytoskeleton rearrangement and dynamics, which subsequently lead to alteration of downstream signaling pathways and variation in fundamental cell properties, such as cell stiffness, cell motility and susceptibility to viral infection. For example, lymphocytic choriomeningitis virus (LCMV) utilized actin filaments to impel the virus to neighboring cells. Moreover, it might force infected cells to migrate faster to approach to the nearest cell [121]; HIV infection changed cytoskeleton composition of glomerular podocyte and resulted in differed cellular stiffness [122]. JEV [36], KSHV [38], Moloney murine leukemia virus (M-MLV), HIV [50], VACV [52] and PHEV [66] infections caused actin filaments rearrangements in multiple ways, which in turn facilitated their infection. Vimentin rearrangements also occurred in many viral infections like parvovirus minute virus of mice (MVM) [123], enterovirus group B virus [124] and African swine fever virus (ASFV) [125].

In addition, viral infection may lead to disruption of cell-cell junctions due to their barrier function against viral infection. Viruses like RSV, Human rhinovirus (HRV), influenza virus and corona virus were able to disrupt tight junctions by targeting several tight junction proteins to facilitate their infection [126]. Adenovirus fiber protein bounded CAR and disrupted tight junction's integrity, facilitating virus apical escape [72]. Ebola virus stimulated Rho/ROCK pathway and then induced actin bundles formation, which generated a tensile force which loosened the VE-cadherin formed inter-cellular junctions [115]. As mentioned previously, cell-cell junctions are indispensable for tissue mechanics. Therefore, disruption of cell-cell junctions by viral infection may lead to mechanical changes at tissue scale.

Together, viral infection and cell mechanics changes are interacting complicatedly with each other. Infection-caused changes of cell mechanics may in turn generate different kinds of effects on different status of viral life cycle.

### 5.3. Organ-on-a-Chip

Organ-on-a-chip provides a practical platform investigating host-pathogens interactions in visual microsystems. In contrast to traditional planar culturing models and animal models, these devices show exceptional advantages including convenient, low volume, low-cost and visibility. Based on available microfluidic tools, there are many unexpected findings that cannot be observed by other virus models. However, these findings are more related to phenomena without revealing detailed mechanisms. Following works will aim to figure out how mechanical forces influence biological behaviors, what is the molecular mechanism during virus infection, which signaling pathways or mechanosensors act as a dominant role regulating mechanobiological responses.

What's more, from mechanobiological standpoint, there are still new landscapes waiting to be discovered. Owing to sophisticated interplays between mechanical forces and cells during virus infection, microsystems with more bionic structures need to be developed to better understand the mechanisms of mechanobiology in virology.

**Author Contributions:** Conceptualization, Y.J. and Y-J.L.; writing—original draft preparation, W.L. and D.T; writing—review and editing, Y.J. and Y-J.L.; supervision, Y.J. and Y-J.L.; funding acquisition, Y.J. and Y-J.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by CAS-VPST Silk Road Science Fund (GJHZ2021138); National Natural Science Foundation of China (Grant No. 92054104, 31970660 and 31870978); Shanghai Municipal Science and Technology Major Project (2019SHZDZX02); “100 talents program” from the Chinese Academy of Sciences; and Key Laboratory of Molecular Virology & Immunology, Institut Pasteur of Shanghai (KLMVI-OP-202001).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## Appendix A

A list of abbreviations for viruses

Abbreviation	Full name
MLV	Murine leukemia virus
HSV	Herpes simplex virus
JEV	Japanese encephalitis virus
WNV	West Nile virus
KSHV	Kaposi's sarcoma-associated herpesvirus
HIV-1	human immunodeficiency virus-1
HTNV	Hantaan virus
ANDV	Andes orthohantavirus
SV40	Simian virus 40
TGEV	Transmissible gastroenteritis virus
IAV	Influenza A virus
VACV	Vaccinia virus
MV	Measles virus
HPV16-PsVs	Human papillomavirus 16 pseudovirions
PHEV	Porcine hemagglutinating encephalomyelitis virus
ZIKV	Zika virus
AAV	Adeno-associated virus
HCV	Hepatitis C virus
RSV	Respiratory syncytial virus
PIV-5	Paramyxovirus parainfluenza virus 5
hPIV-2	Human parainfluenza virus type 2
HCMV	Human cytomegalovirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
HBV	Hepatitis B virus
CVB1	Coxsackievirus B1
HRV-16	Human rhinovirus strain 16
LCMV	Lymphocytic choriomeningitis virus
M-MLV	Moloney murine leukemia virus
MVM	Parvovirus minute virus of mice
ASFV	African swine fever virus

## HRV

## Human rhinovirus

## References

1. Krieg, M.; Fläschner, G.; Alsteens, D.; Gaub, B.M.; Roos, W.H.; Wuite, G.J.L.; Gaub, H.E.; Gerber, C.; Dufrière, Y.F.; Müller, D.J. Atomic force microscopy-based mechanobiology. *Nat. Rev. Phys.* **2019**, *1*, 41–57, doi:10.1038/s42254-018-0001-7.
2. Howard, J.; Grill, S.W.; Bois, J.S. Turing's next steps: The mechanochemical basis of morphogenesis. *Nat. Rev. Mol. Cell Biol.* **2011**, *12*, 400–406, doi:10.1038/nrm3120.
3. Eyckmans, J.; Boudou, T.; Yu, X.; Chen, C.S. A Hitchhiker's Guide to Mechanobiology. *Dev. Cell* **2011**, *21*, 35–47, doi:10.1016/j.devcel.2011.06.015.
4. Schwarz, U.S. Mechanobiology by the numbers: A close relationship between biology and physics. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 711–712, doi:10.1038/nrm.2017.109.
5. Polacheck, W.J.; Li, R.; Uzel, S.G.M.; Kamm, R.D. Microfluidic platforms for mechanobiology. *Lab Chip* **2013**, *13*, 2252–2267, doi:10.1039/c3lc41393d.
6. Naruse, K. Mechanomedicine: Applications of mechanobiology to medical sciences and next-generation medical technologies. *J. Smooth Muscle Res.* **2018**, *54*, 83–90, doi:10.1540/JSMR.54.83.
7. Wang, N.; Butler, J.P.; Ingber, D.E. Mechanotransduction Across the Cell Surface and Through the Cytoskeleton. *Science* **1993**, *260*, 1124–1128, doi:10.1126/science.7684161.
8. Vining, K.H.; Mooney, D.J. Mechanical forces direct stem cell behaviour in development and regeneration. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 728–742, doi:10.1038/nrm.2017.108.
9. Hohmann, T.; Dehghani, F. The Cytoskeleton—A Complex Interacting Meshwork. *Cells* **2019**, *8*, 362, doi:10.3390/cells8040362.
10. Goodson, H. V.; Jonasson, E.M. Microtubules and microtubule-associated proteins. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, doi:10.1101/cshperspect.a022608.
11. Blanchoin, L.; Boujemaa-Paterski, R.; Sykes, C.; Plastino, J. Actin dynamics, architecture, and mechanics in cell motility. *Physiol. Rev.* **2014**, *94*, 235–263, doi:10.1152/physrev.00018.2013.
12. Goldmann, W.H. Intermediate filaments and cellular mechanics. *Cell Biol. Int.* **2018**, *42*, 132–138, doi:10.1002/cbin.10879.
13. Fletcher, D.A.; Mullins, R.D. Cell mechanics and the cytoskeleton. *Nature* **2010**, *463*, 485–492, doi:10.1038/nature08908.
14. Gregor, M.; Osmanagic-Myers, S.; Burgstaller, G.; Wolfram, M.; Fischer, I.; Walko, G.; Resch, G.P.; Jörgl, A.; Herrmann, H.; Wiche, G. Mechanosensing through focal adhesion-anchored intermediate filaments. *FASEB J.* **2014**, *28*, 715–729, doi:10.1096/fj.13-231829.
15. Petit, V.; Thiery, J.P. Focal adhesions: Structure and dynamics. *Biol. Cell* **2000**, *92*, 477–494, doi:10.1016/S0248-4900(00)01101-1.
16. Garcia, M.A.; Nelson, W.J.; Chavez, N. Cell–cell junctions organize structural and signaling networks. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, doi:10.1101/cshperspect.a029181.
17. Yap, A.S.; Duszyc, K.; Viasnoff, V. Mechanosensing and mechanotransduction at cell –cell junctions. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, doi:10.1101/cshperspect.a028761.
18. Sinha, B.; Köster, D.; Ruez, R.; Gonnord, P.; Bastiani, M.; Abankwa, D.; Stan, R. V.; Butler-Browne, G.; Védie, B.; Johannes, L.; et al. Cells respond to mechanical stress by rapid disassembly of caveolae. *Cell* **2011**, *144*, 402–413, doi:10.1016/j.cell.2010.12.031.
19. Xing, Y.; Wen, Z.; Gao, W.; Lin, Z.; Zhong, J.; Jiu, Y. Multifaceted Functions of Host Cell Caveolae/Caveolin-1 in Virus Infections. *Viruses* **2020**, *12*, 487, doi:10.3390/v12050487.

20. Souilhoul, C.; Serbanovic-Canic, J.; Fragiadaki, M.; Chico, T.J.; Ridger, V.; Roddie, H.; Evans, P.C. Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes. *Nat. Rev. Cardiol.* **2020**, *17*, 52–63, doi:10.1038/s41569-019-0239-5.
21. Villenave, R.; Wales, S.Q.; Hamkins-Indik, T.; Papafragkou, E.; Weaver, J.C.; Ferrante, T.C.; Bahinski, A.; Elkins, C.A.; Kulka, M.; Ingber, D.E. Human gut-on-a-chip supports polarized infection of coxsackie B1 virus in vitro. *PLoS One* **2017**, *12*, 1–17, doi:10.1371/journal.pone.0169412.
22. Schutte, A.E.; Kruger, R.; Gafane-Matemane, L.F.; Breet, Y.; Strauss-Kruger, M.; Cruickshank, J.K. Ethnicity and Arterial Stiffness. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 1044–1054, doi:10.1161/ATVBAHA.120.313133.
23. Vinikoor, M.J.; Mulenga, L.; Siyunda, A.; Musukuma, K.; Chilengi, R.; Moore, C.B.; Chi, B.H.; Davies, M.A.; Egger, M.; Wandeler, G. Association between hepatitis B co-infection and elevated liver stiffness among HIV-infected adults in Lusaka, Zambia. *Trop. Med. Int. Heal.* **2016**, *21*, 1435–1441, doi:10.1111/tmi.12764.
24. Xu, N.; Wang, J.; Zhang, Z.F.; Pang, D.W.; Wang, H.Z.; Zhang, Z.L. Anisotropic cell-to-cell spread of vaccinia virus on microgrooved substrate. *Biomaterials* **2014**, *35*, 5049–5055, doi:10.1016/j.biomaterials.2014.03.019.
25. Si, L.; Bai, H.; Rodas, M.; Cao, W.; Oh, C.Y.; Jiang, A.; Nurani, A.; Zhu, D.; Goyal, G.; Gilpin, S.; et al. Human organs-on-chips as tools for repurposing approved drugs as potential influenza and COVID19 therapeutics in viral pandemics. *bioRxiv* **2020**, doi:10.1101/2020.04.13.039917.
26. Kang, Y.B.A.; Sodunke, T.R.; Lamontagne, J.; Cirillo, J.; Rajiv, C.; Bouchard, M.J.; Noh, M. Liver sinusoid on a chip: Long-term layered co-culture of primary rat hepatocytes and endothelial cells in microfluidic platforms. *Biotechnol. Bioeng.* **2015**, *112*, 2571–2582, doi:10.1002/bit.25659.
27. Ortega-Prieto, A.M.; Skelton, J.K.; Wai, S.N.; Large, E.; Lussignol, M.; Vizcay-Barrena, G.; Hughes, D.; Fleck, R.A.; Thursz, M.; Catanese, M.T.; et al. 3D microfluidic liver cultures as a physiological preclinical tool for hepatitis B virus infection. *Nat. Commun.* **2018**, *9*, 682, doi:10.1038/s41467-018-02969-8.
28. Spear, M.; Wu, Y. Viral exploitation of actin: Force-generation and scaffolding functions in viral infection. *Virol. Sin.* **2014**, *29*, 139–147, doi:10.1007/s12250-014-3476-0.
29. Lehmann, M.J.; Sherer, N.M.; Marks, C.B.; Pypaert, M.; Mothes, W. Actin- and myosin-driven movement of viruses along filopodia precedes their entry into cells. *J. Cell Biol.* **2005**, *170*, 317–325, doi:10.1083/jcb.200503059.
30. Salameh, S. Early Events in Herpes Simplex Virus Lifecycle with Implications for an Infection of Lifetime. *Open Virol. J.* **2012**, *6*, 1–6, doi:10.2174/1874357901206010001.
31. Mercer, J.; Lee, J.E.; Saphire, E.O.; Freeman, S.A. SnapShot: Enveloped Virus Entry. *Cell* **2020**, *182*, 786, doi:10.1016/j.cell.2020.06.033.
32. Mercer, J.; Schelhaas, M.; Helenius, A. Virus entry by endocytosis. *Annu. Rev. Biochem.* **2010**, *79*, 803–833, doi:10.1146/annurev-biochem-060208-104626.
33. Kaksonen, M.; Toret, C.P.; Drubin, D.G. Harnessing actin dynamics for clathrin-mediated endocytosis. *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 404–414, doi: 10.1038/nrm1940.
34. Guo, Y.; Duan, M.; Wang, X.; Gao, J.; Guan, Z.; Zhang, M. Early events in rabies virus infection – Attachment, entry, and intracellular trafficking. *Virus Res.* **2019**, *263*, 217–255, doi:10.1016/j.virusres.2019.02.006.
35. Meier, O.; Greber, U.F. Adenovirus endocytosis. *J. Gene Med.* **2004**, *6*, S152–S163, doi:10.1002/jgm.553.
36. Kalia, M.; Khasa, R.; Sharma, M.; Nain, M.; Vrati, S. Japanese Encephalitis Virus Infects Neuronal Cells through a Clathrin-Independent Endocytic Mechanism. *J. Virol.* **2013**, *87*, 148–162, doi:10.1128/jvi.01399-12.
37. Chu, J.J.H.; Leong, P.W.H.; Ng, M.L. Analysis of the endocytic pathway mediating the infectious entry of mosquito-borne flavivirus West Nile into *Aedes albopictus* mosquito (C6/36) cells. *Virology* **2006**, *349*, 463–475, doi:10.1016/j.virol.2006.01.022.

38. Greene, W.; Gao, S.J. Actin dynamics regulate multiple endosomal steps during Kaposi's sarcoma-associated herpesvirus entry and trafficking in endothelial cells. *PLoS Pathog.* **2009**, *5*, e1000512, doi:10.1371/journal.ppat.1000512.
39. King, J.S.; Kay, R.R. The origins and evolution of macropinocytosis. *Philos. Trans. R. Soc. B Biol. Sci.* **2019**, *374*, doi:10.1098/rstb.2018.0158.
40. Veetti, M.V.; Sadagopan, S.; Kerur, N.; Chakraborty, S.; Chandran, B. Interaction of c-Cbl with myosin IIA regulates bleb associated macropinocytosis of Kaposi's sarcoma-associated herpesvirus. *PLoS Pathog.* **2010**, *6*, e1001238, doi:10.1371/journal.ppat.1001238.
41. Ménager, M.M. TSPAN7, effector of actin nucleation required for dendritic cell-mediated transfer of HIV-1 to T cells. *Biochem. Soc. Trans.* **2017**, *45*, 703–708, doi:10.1042/BST20160439.
42. Torriani, G.; Mayor, J.; Zimmer, G.; Kunz, S.; Rothenberger, S.; Engler, O. Macropinocytosis contributes to hantavirus entry into human airway epithelial cells. *Virology* **2019**, *531*, 57–68, doi:10.1016/j.virol.2019.02.013.
43. Hinze, C.; Boucrot, E. Local actin polymerization during endocytic carrier formation. *Biochem. Soc. Trans.* **2018**, *46*, 565–576, doi:10.1042/BST20170355.
44. Pelkmans, L.; Helenius, A. Endocytosis via caveolae. *Traffic* **2002**, *3*, 311–320, doi:10.1034/j.1600-0854.2002.30501.x.
45. Wang, J.; Li, Y.; Wang, S.; Liu, F. Dynamics of transmissible gastroenteritis virus internalization unraveled by single-virus tracking in live cells. *FASEB J.* **2020**, *34*, 4653–4669, doi:10.1096/fj.201902455R.
46. Banerjee, I.; Miyake, Y.; Philip Nobs, S.; Schneider, C.; Horvath, P.; Kopf, M.; Matthias, P.; Helenius, A.; Yamauchi, Y. Influenza A virus uses the aggresome processing machinery for host cell entry. *Science.* **2014**, *346*, 473–477, doi:10.1126/science.1257037.
47. Wen, Z.; Zhang, Y.; Lin, Z.; Shi, K.; Jiu, Y. Cytoskeleton-a crucial key in host cell for coronavirus infection. *J. Mol. Cell Biol.* **2021**, *12*, 968–979, doi:10.1093/jmcb/mjaa042.
48. Spear, M.; Guo, J.; Turner, A.; Yu, D.; Wang, W.; Meltzer, B.; He, S.; Hu, X.; Shang, H.; Kuhn, J.; et al. HIV-1 triggers WAVE2 phosphorylation in primary CD4 T cells and macrophages, mediating Arp2/3-dependent nuclear migration. *J. Biol. Chem.* **2014**, *289*, 6949–6959, doi:10.1074/jbc.M113.492132.
49. Schramm, B.; de Haan, C.A.M.; Young, J.; Doglio, L.; Schleich, S.; Reese, C.; Popov, A. V.; Steffen, W.; Schroer, T.; Locker, J.K. Vaccinia-virus-induced cellular contractility facilitates the subcellular localization of the viral replication sites. *Traffic* **2006**, *7*, 1352–1367, doi:10.1111/j.1600-0854.2006.00470.x.
50. Gladnikoff, M.; Shimoni, E.; Gov, N.S.; Rousso, I. Retroviral assembly and budding occur through an actin-driven mechanism. *Biophys. J.* **2009**, *97*, 2419–2428, doi:10.1016/j.bpj.2009.08.016.
51. Newsome, T.P.; Marzook, N.B. Viruses that ride on the coat-tails of actin nucleation. *Semin. Cell Dev. Biol.* **2015**, *46*, 155–163, doi:10.1016/j.semcdb.2015.10.008.
52. Horsington, J.; Lynn, H.; Turnbull, L.; Cheng, D.; Braet, F.; Diefenbach, R.J.; Whitchurch, C.B.; Karupiah, G.; Newsome, T.P. A36-dependent Actin Filament Nucleation Promotes Release of Vaccinia Virus. *PLoS Pathog.* **2013**, *9*, e1003239, doi:10.1371/journal.ppat.1003239.
53. Bohn, W.; Rutter, G.; Hohenberg, H.; Mannweiler, K.; Nobis, P. Involvement of actin filaments in budding of measles virus: Studies on cytoskeletons of infected cells. *Virology* **1986**, *149*, 91–106, doi:10.1016/0042-6822(86)90090-5.
54. Chu, J.J.H.; Choo, B.G.H.; Lee, J.W.M.; Ng, M.L. Actin filaments participate in West Nile (Sarafend) virus maturation process. *J. Med. Virol.* **2003**, *71*, 463–472, doi:10.1002/jmv.10495.
55. Ng, M.L.; Lee, J.W.M.; Leong, M.L.N.; Ling, A.E.; Tan, H.C.; Ooi, E.E. Topographic changes in SARS coronavirus-infected cells during late stages of infection. *Emerg. Infect. Dis.* **2004**, *10*, 1907–1914, doi:10.3201/eid1011.040195.
56. Das, P.; Saha, S.; Chandra, S.; Das, A.; Dey, S.K.; Das, M.R.; Sen, S.; Sarkar, D.P.; Jana, S.S. Phosphorylation of nonmuscle myosin II-A regulatory light chain resists Sendai virus fusion with host cells. *Sci. Rep.* **2015**, *5*, 10395, doi:10.1038/srep10395.

57. Uhler, C.; Shivashankar, G. V. Regulation of genome organization and gene expression by nuclear mechanotransduction. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 717–727, doi:10.1038/nrm.2017.101.
58. Sanghvi-Shah, R.; Weber, G.F. Intermediate filaments at the junction of mechanotransduction, migration, and development. *Front. Cell Dev. Biol.* **2017**, *5*, 81, doi:10.3389/fcell.2017.00081.
59. Laly, A.C.; Sliogeryte, K.; Pundel, O.J.; Ross, R.; Keeling, M.C.; Avisetti, D.; Waseem, A.; Gavara, N.; Connelly, J.T. The keratin network of intermediate filaments regulates keratinocyte rigidity sensing and nuclear mechanotransduction. *Sci. Adv.* **2021**, *7*, eabd6187, doi:10.1126/sciadv.abd6187.
60. Yu, Y.T.C.; Chien, S.C.; Chen, I.Y.; Lai, C.T.; Tsay, Y.G.; Chang, S.C.; Chang, M.F. Surface vimentin is critical for the cell entry of SARS-CoV. *J. Biomed. Sci.* **2016**, *23*, 14, doi:10.1186/s12929-016-0234-7.
61. Schäfer, G.; Graham, L.M.; Lang, D.M.; Blumenthal, M.J.; Bergant Marušič, M.; Katz, A.A. Vimentin Modulates Infectious Internalization of Human Papillomavirus 16 Pseudovirions. *J. Virol.* **2017**, *91*, 1-17, doi:10.1128/jvi.00307-17.
62. Wu, W.; Panté, N. Vimentin plays a role in the release of the influenza A viral genome from endosomes. *Virology* **2016**, *497*, 41–52, doi:10.1016/j.virol.2016.06.021.
63. Shyy, J.Y.J.; Chien, S. Role of integrins in endothelial mechanosensing of shear stress. *Circ. Res.* **2002**, *91*, 769–775, doi:10.1161/01.RES.0000038487.19924.18.
64. Zhou, J.; Aponte-Santamaría, C.; Sturm, S.; Bullerjahn, J.T.; Bronowska, A.; Gräter, F. Mechanism of Focal Adhesion Kinase Mechanosensing. *PLoS Comput. Biol.* **2015**, *11*, e1004593, doi:10.1371/journal.pcbi.1004593.
65. Petzold, T.; Orr, A.W.; Hahn, C.; Jhaveri, K.A.; Parsons, J.T.; Schwartz, M.A. Focal adhesion kinase modulates activation of NF- $\kappa$ B by flow in endothelial cells. *Am. J. Physiol. Cell Physiol.* **2009**, *297*, C814–C822, doi:10.1152/ajpcell.00226.2009.
66. Lv, X.; Li, Z.; Guan, J.; Hu, S.; Zhang, J.; Lan, Y.; Zhao, K.; Lu, H.; Song, D.; He, H.; et al. Porcine Hemagglutinating Encephalomyelitis Virus Activation of the Integrin  $\alpha$ 5 $\beta$ 1-FAK-Cofilin Pathway Causes Cytoskeletal Rearrangement To Promote Its Invasion of N2a Cells. *J. Virol.* **2018**, *93*, 1–19, doi:10.1128/jvi.01736-18.
67. Bergmann, S.; Elbahesh, H. Targeting the proviral host kinase, FAK, limits influenza a virus pathogenesis and NF $\kappa$ B-regulated pro-inflammatory responses. *Virology* **2019**, *534*, 54–63, doi:10.1016/j.virol.2019.05.020.
68. Bogachek, M. V.; Zaitsev, B.N.; Sekatskii, S.K.; Protopopova, E. V.; Ternovoi, V.A.; Ivanova, A. V.; Kachko, A. V.; Ivanisenko, V.A.; Dietler, G.; Loktev, V.B. Characterization of glycoprotein E C-end of west nile virus and evaluation of its interaction force with  $\alpha$ v $\beta$ 3 integrin as putative cellular receptor. *Biochem.* **2010**, *75*, 472–480, doi:10.1134/S0006297910040115.
69. Wang, S.; Zhang, Q.; Tiwari, S.K.; Lichinchi, G.; Yau, E.H.; Hui, H.; Li, W.; Furnari, F.; Rana, T.M. Integrin  $\alpha$ v $\beta$ 5 Internalizes Zika Virus during Neural Stem Cells Infection and Provides a Promising Target for Antiviral Therapy. *Cell Rep.* **2020**, *30*, 969-983.e4, doi:10.1016/j.celrep.2019.11.020.
70. Summerford, C.; Bartlett, J.S.; Samulski, R.J.  $\alpha$ v $\beta$ 5 integrin: A co-receptor for adeno-associated virus type 2 infection. *Nat. Med.* **1999**, *5*, 78-82, doi:10.1038/4768.
71. Lyle, C.; McCormick, F. Integrin  $\alpha$ v $\beta$ 5 is a primary receptor for adenovirus in CAR-negative cells. *Virol. J.* **2010**, *7*, 148, doi:10.1186/1743-422X-7-148.
72. Walters, R.W.; Freimuth, P.; Moninger, T.O.; Ganske, I.; Zabner, J.; Welsh, M.J. Adenovirus fiber disrupts CAR-mediated intercellular adhesion allowing virus escape. *Cell* **2002**, *110*, 789–799, doi:10.1016/S0092-8674(02)00912-1.
73. Evans, M.J.; Von Hahn, T.; Tschernhe, D.M.; Syder, A.J.; Panis, M.; Wölk, B.; Hatzioannou, T.; McKeating, J.A.; Bieniasz, P.D.; Rice, C.M. Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. *Nature* **2007**, *446*, 801–805, doi:10.1038/nature05654.
74. Mühlebach, M.D.; Mateo, M.; Sinn, P.L.; Prüfer, S.; Uhlig, K.M.; Leonard, V.H.J.; Navaratnarajah, C.K.; Frenzke, M.; Wong, X.X.; Sawatsky, B.; et al. Adherens junction protein nectin-4 is the epithelial receptor for measles virus. *Nature* **2011**, *480*, 530-533, doi:10.1038/nature10639.

75. Boyd, N.L.; Park, H.; Yi, H.; Boo, Y.C.; Sorescu, G.P.; Sykes, M.; Jo, H. Chronic shear induces caveolae formation and alters ERK and Akt responses in endothelial cells. *Am. J. Physiol. Hear. Circ. Physiol.* **2003**, *285*, 1113–1122, doi:10.1152/ajpheart.00302.2003.
76. Echarri, A.; Del Pozo, M.A. Caveolae - mechanosensitive membrane invaginations linked to actin filaments. *J. Cell Sci.* **2015**, *128*, 2747–2758, doi:10.1242/jcs.153940.
77. Wang, X.M.; Nadeau, P.E.; Lo, Y.-T.; Mergia, A. Caveolin-1 Modulates HIV-1 Envelope-Induced Bystander Apoptosis through gp41. *J. Virol.* **2010**, *84*, 6515–6526, doi:10.1128/jvi.02722-09.
78. Ludwig, A.; Nguyen, T.H.; Leong, D.; Ravi, L.I.; Tan, B.H.; Sandin, S.; Sugrue, R.J. Caveolae provide a specialized membrane environment for respiratory syncytial virus assembly. *J. Cell Sci.* **2017**, *130*, 1037–1050, doi:10.1242/jcs.198853.
79. Ravid, D.; Leser, G.P.; Lamb, R.A. A Role for Caveolin 1 in Assembly and Budding of the Paramyxovirus Parainfluenza Virus 5. *J. Virol.* **2010**, *84*, 9749–9759, doi:10.1128/jvi.01079-10.
80. Ohta, K.; Matsumoto, Y.; Nishio, M. Inhibition of Cavin3 Degradation by the Human Parainfluenza Virus Type 2 V Protein Is Important for Efficient Viral Growth. *Front. Microbiol.* **2020**, *11*, 803, doi:10.3389/fmicb.2020.00803.
81. Tang, H.; Abouleila, Y.; Si, L.; Ortega-Prieto, A.M.; Mummery, C.L.; Ingber, D.E.; Mashaghi, A. Human Organs-on-Chips for Virology. *Trends Microbiol.* **2020**, *28*, 934–946, doi:10.1016/j.tim.2020.06.005.
82. Traub, O.; Berk, B.C. Laminar shear stress: Mechanisms by which endothelial cells transduce an atheroprotective force. *Arterioscler. Thromb. Vasc. Biol.* **1998**, *18*, 677–685, doi:10.1161/01.ATV.18.5.677.
83. Tonkin, M.L.; Boulanger, M.J. The Shear Stress of Host Cell Invasion: Exploring the Role of Biomolecular Complexes. *PLoS Pathog.* **2015**, *11*, 1–7, doi:10.1371/journal.ppat.1004539.
84. Jacob, H.S. Vascular shear forces and atherogenesis: Roles of shear-provoked endothelial viral infection and heme iron accumulation. *Perspect. Biol. Med.* **1994**, *38*, 114–124, doi:10.1353/pbm.1994.0011.
85. DuRose, J.B.; Li, J.; Chien, S.; Spector, D.H. Infection of Vascular Endothelial Cells with Human Cytomegalovirus under Fluid Shear Stress Reveals Preferential Entry and Spread of Virus in Flow Conditions Simulating Atheroprone Regions of the Artery. *J. Virol.* **2012**, *86*, 13745–13755, doi:10.1128/jvi.02244-12.
86. Kaneko, N.; Satta, S.; Komuro, Y.; Muthukrishnan, S.D.; Kakarla, V.; Guo, L.; An, J.; Elahi, F.; Kornblum, H.I.; Liebeskind, D.S.; et al. Flow-Mediated Susceptibility and Molecular Response of Cerebral Endothelia to SARS-CoV-2 Infection. *Stroke* **2021**, 260–270, doi:10.1161/STROKEAHA.120.032764.
87. Kim, J.A.; Choi, H.J.; Kim, C.M.; Jin, H.K.; Bae, J. sung; Kim, G.M. Enhancement of virus infection using dynamic cell culture in a microchannel. *Micromachines* **2018**, *9*, 1–11, doi:10.3390/mi9100482.
88. Grein, T.A.; Loewe, D.; Dieken, H.; Weidner, T.; Salzig, D.; Czermak, P. Aeration and Shear Stress Are Critical Process Parameters for the Production of Oncolytic Measles Virus. *Front. Bioeng. Biotechnol.* **2019**, *7*, 1–11, doi:10.3389/fbioe.2019.00078.
89. Wu, S.C.; Huang, G.Y.L. Hydrodynamic shear forces increase Japanese encephalitis virus production from microcarrier-grown Vero cells. *Bioprocess Eng.* **2000**, *23*, 229–233, doi:10.1007/s004499900156.
90. Weidner, T.; Druzinec, D.; Mühlmann, M.; Buchholz, R.; Czermak, P. The components of shear stress affecting insect cells used with the baculovirus expression vector system. *Zeitschrift für Naturforsch. Sect. C J. Biosci.* **2017**, *72*, 429–439, doi:10.1515/znc-2017-0066.
91. Sackner, M.A.; Adams, J.A. Endothelial pulsatile shear stress is a backstop for COVID-19. *Emerg. Top. Life Sci.* **2020**, *4*, 391–399, doi:10.1042/ETLS20200260.
92. Sanderson, C.M.; Way, M.; Smith, G.L. Virus-Induced Cell Motility. *Microbiology* **1998**, *72*, 1235–1243, doi:10.1128/JVI.72.2.1235-1243.1998.

93. Wang, C.; Xu, N.; Yang, Y.J.; Wu, Q.M.; Pang, D.W.; Zhang, Z.L. Enhanced directional cell migration induced by vaccinia virus on a microfluidic-based multi-shear cell migration assay platform. *Integr. Biol.* **2017**, *9*, 903–911, doi:10.1039/c7ib00151g.
94. Wang, J.; Wang, C.; Xu, N.; Liu, Z.F.; Pang, D.W.; Zhang, Z.L. A virus-induced kidney disease model based on organ-on-a-chip: Pathogenesis exploration of virus-related renal dysfunctions. *Biomaterials* **2019**, *219*, 119367, doi:10.1016/j.biomaterials.2019.119367.
95. Fink, J.; Carpi, N.; Betz, T.; Bétard, A.; Chebah, M.; Azioune, A.; Bornens, M.; Sykes, C.; Fetler, L.; Cuvelier, D.; et al. External forces control mitotic spindle positioning. *Nat. Cell Biol.* **2011**, *13*, 771–778, doi:10.1038/ncb2269.
96. Chaudhuri, P.K.; Low, B.C.; Lim, C.T. Mechanobiology of Tumor Growth. *Chem. Rev.* **2018**, *118*, 6499–6515, doi:10.1021/acs.chemrev.8b00042.
97. Racaniello, V.R. One hundred years of poliovirus pathogenesis. *Virology* **2006**, *344*, 9–16, doi:10.1016/j.virol.2005.09.015.
98. Bettinger, C.J.; Langer, R.; Borenstein, J.T. Engineering substrate topography at the Micro- and nanoscale to control cell function. *Angew. Chemie Int. Ed.* **2009**, *48*, 5406–5415, doi:10.1002/anie.200805179.
99. Ghibaudo, M.; Trichet, L.; Le Digabel, J.; Richert, A.; Hersen, P.; Ladoux, B. Substrate topography induces a crossover from 2D to 3D behavior in fibroblast migration. *Biophys. J.* **2009**, *97*, 357–368, doi:10.1016/j.bpj.2009.04.024.
100. Wang, C.; Wang, J.; Fu, D.; Yan, Q.; Pang, D.; Zhang, Z. Topography guiding the accelerated and persistently directional cell migration induced by vaccinia virus. *Chinese Chem. Lett.* **2019**, *31*, 161–171, doi:10.1016/j.ccl.2019.05.043.
101. Huh, D.; Matthews, B.D.; Mammoto, A.; Montoya-Zavala, M.; Yuan Hsin, H.; Ingber, D.E. Reconstituting organ-level lung functions on a chip. *Science* **2010**, *328*, 1662–1668, doi:10.1126/science.1188302.
102. Benam, K.H.; Villenave, R.; Lucchesi, C.; Varone, A.; Hubeau, C.; Lee, H.H.; Alves, S.E.; Salmon, M.; Ferrante, T.C.; Weaver, J.C.; et al. Small airway-on-a-chip enables analysis of human lung inflammation and drug responses in vitro. *Nat. Methods* **2016**, *13*, 151–157, doi:10.1038/nmeth.3697.
103. Si, L.; Prantil-Baun, R.; Benam, K.H.; Bai, H.; Rodas, M.; Burt, M.; Ingber, D.E. Discovery of influenza drug resistance mutations and host therapeutic targets using a human airway chip. *bioRxiv* **2019**, doi:10.1101/685552.
104. Deinhardt-Emmer, S.; Rennert, K.; Schicke, E.; Cseresnyés, Z.; Windolph, M.; Nietzsche, S.; Heller, R.; Siwczak, F.; Haupt, K.F.; Carlstedt, S.; et al. Co-infection with *Staphylococcus aureus* after primary influenza virus infection leads to damage of the endothelium in a human alveolus-on-a-chip model. *Biofabrication* **2020**, *12*, 025012, doi:10.1088/1758-5090/ab7073.
105. Zhang, M.; Wang, P.; Luo, R.; Wang, Y.; Li, Z.; Guo, Y.; Yao, Y.; Li, M.; Tao, T.; Chen, W.; et al. Biomimetic Human Disease Model of SARS-CoV-2-Induced Lung Injury and Immune Responses on Organ Chip System. *Adv. Sci.* **2021**, *8*, 1–14, doi:10.1002/advs.202002928.
106. Nawroth, J.C.; Lucchesi, C.; Cheng, D.; Shukla, A.; Ngyuen, J.; Shroff, T.; Varone, A.; Karalis, K.; Lee, H.H.; Alves, S.; et al. A Microengineered Airway Lung- chip Models Key Features of Viral-induced Exacerbation of Asthma. *Am. J. Respir. Cell Mol. Biol.* **2020**, *63*, 591–600, doi:10.1165/RCMB.2020-0010MA.
107. Wohlleber, D.; Knolle, P.A. The role of liver sinusoidal cells in local hepatic immune surveillance. *Clin. Transl. Immunol.* **2016**, *5*, e117, doi:10.1038/cti.2016.74.
108. Nahmias, Y.; Berthiaume, F.; Yarmush Martin L. *Tissue Engineering II: Basics of Tissue Engineering and Tissue Applications*; Springer: New York, USA, 2007; pp. 309-329.
109. Rowe, C.; Gerrard, D.T.; Jenkins, R.; Berry, A.; Durkin, K.; Sundstrom, L.; Goldring, C.E.; Park, B.K.; Kitteringham, N.R.; Hanley, K.P.; et al. Proteome-wide analyses of human hepatocytes during differentiation and dedifferentiation. *Hepatology* **2013**, *58*, 799–809, doi:10.1002/hep.26414.
110. Chen, Y.; Wong, P.P.; Sjeklocha, L.; Steer, C.J.; Sahin, M.B. Mature hepatocytes exhibit unexpected plasticity by direct dedifferentiation into liver progenitor cells in culture. *Hepatology* **2012**, *55*, 563–574, doi:10.1002/hep.24712.

111. Kang, Y.B.; Rawat, S.; Duchemin, N.; Bouchard, M.; Noh, M. Human liver sinusoid on a chip for hepatitis B virus replication study. *Micromachines* **2017**, *8*, 1–13, doi:10.3390/mi8010027.
112. Ortega-Prieto, A.M.; Skelton, J.K.; Cherry, C.; Briones-Orta, M.A.; Hateley, C.A.; Dorner, M. “Liver-on-a-Chip” Cultures of Primary Hepatocytes and Kupffer Cells for Hepatitis B Virus Infection. *J. Vis. Exp.* **2019**, 1–9, doi:10.3791/58333.
113. Barrila, J.; Crabbé, A.; Yang, J.; Franco, K.; Nydam, S.D.; Forsyth, R.J.; Davis, R.R.; Gangaraju, S.; Mark Ott, C.; Coyne, C.B.; et al. Modeling host-pathogen interactions in the context of the microenvironment: Three-dimensional cell culture comes of age. *Infect. Immun.* **2018**, *86*, 1–28, doi:10.1128/IAI.00282-18.
114. Kim, H.J.; Li, H.; Collins, J.J.; Ingber, D.E. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, E7–E15, doi:10.1073/pnas.1522193112.
115. Junaid, A.; Tang, H.; van Reeuwijk, A.; Abouleila, Y.; Wuelfroth, P.; van Duinen, V.; Stam, W.; van Zonneveld, A.J.; Hankemeier, T.; Mashaghi, A. Ebola Hemorrhagic Shock Syndrome-on-a-Chip. *iScience* **2020**, *23*, 100765, doi:10.1016/j.isci.2019.100765.
116. Mack, J.J.; Mosqueiro, T.S.; Archer, B.J.; Jones, W.M.; Sunshine, H.; Faas, G.C.; Briot, A.; Aragón, R.L.; Su, T.; Romay, M.C.; et al. NOTCH1 is a mechanosensor in adult arteries. *Nat. Commun.* **2017**, *8*, 1620, doi:10.1038/s41467-017-01741-8.
117. Wang, J.; Shelly, L.; Miele, L.; Boykins, R.; Norcross, M.A.; Guan, E. Human Notch-1 Inhibits NF- $\kappa$ B Activity in the Nucleus Through a Direct Interaction Involving a Novel Domain. *J. Immunol.* **2001**, *167*, 289–295, doi:10.4049/jimmunol.167.1.289.
118. Meng, K.P.; Majedi, F.S.; Thauland, T.J.; Butte, M.J. Mechanosensing through YAP controls T cell activation and metabolism. *J. Exp. Med.* **2020**, *217*, e20200053, doi:10.1084/jem.20200053.
119. Cool, C.D.; Voelkel, N.F.; Bull, T. Viral infection and pulmonary hypertension: Is there an association? *Expert Rev. Respir. Med.* **2011**, *5*, 207–216, doi:10.1586/ers.11.17.
120. Azar, W.S.; Njeim, R.; Fares, A.H.; Azar, N.S.; Azar, S.T.; El Sayed, M.; Eid, A.A. COVID-19 and diabetes mellitus: how one pandemic worsens the other. *Rev. Endocr. Metab. Disord.* **2020**, *21*, 451–463, doi:10.1007/s11154-020-09573-6.
121. Labudová, M.; Čiampor, F.; Pastoreková, S.; Pastorek, J. Cell-to-cell transmission of lymphocytic choriomeningitis virus MX strain during persistent infection and its influence on cell migration. *Acta Virol.* **2018**, *62*, 424–434, doi:10.4149/av\_2018\_411.
122. Tandon, R.; Levental, I.; Huang, C.; Byfield, F.J.; Ziembicki, J.; Schelling, J.R.; Bruggeman, L.A.; Sedor, J.R.; Janmey, P.A.; Miller, R.T. HIV infection changes glomerular podocyte cytoskeletal composition and results in distinct cellular mechanical properties. *Am. J. Physiol. Ren. Physiol.* **2007**, *292*, 701–710, doi:10.1152/ajprenal.00246.2006.
123. Fay, N.; Panté, N. The intermediate filament network protein, vimentin, is required for parvoviral infection. *Virology* **2013**, *444*, 181–190, doi:10.1016/j.virol.2013.06.009.
124. Turkki, P.; Laajala, M.; Flodström-Tullberg, M.; Marjomäki, V. Human Enterovirus Group B Viruses Rely on Vimentin Dynamics for Efficient Processing of Viral Nonstructural Proteins. *J. Virol.* **2019**, *94*, 1–19, doi:10.1128/jvi.01393-19.
125. Stefanovic, S.; Windsor, M.; Nagata, K.; Inagaki, M.; Wileman, T. Vimentin Rearrangement during African Swine Fever Virus Infection Involves Retrograde Transport along Microtubules and Phosphorylation of Vimentin by Calcium Calmodulin Kinase II. *J. Virol.* **2005**, *79*, 11766–11775, doi:10.1128/jvi.79.18.11766-11775.2005.
126. Linfield, D.T.; Raduka, A.; Aghapour, M.; Rezaee, F. Airway tight junctions as targets of viral infections: Tight Junctions and Viral Infections. *Tissue Barriers* **2021**, *9*, e1883965, doi:10.1080/21688370.2021.1883965.