manipulating the magnetic moment produced by the electrons' orbital angular momentum (instead of their spin), thereby bypassing the need for materials with strong spin–orbit coupling. This approach expands the range of materials in which the magnetic moment of electrons can be controlled electrically.

The orbital Hall effect was first proposed[4] in 2005, but making use of it has proved challenging. Part of the problem is that it is difficult to distinguish the magnetic moments arising from orbital angular momentum from those associated with spin. To circumvent this issue, Choi and colleagues used titanium, a lightweight metal with weak spin–orbit coupling and a negligible spin Hall effect. Titanium itself does not have substantial benefits over metals with strong spin–orbit coupling, apart from the fact that it is much more abundant in Earth's crust than are these metals. But the authors' proof of principle shows the feasibility of orbitronics, which could be used to manipulate orbitals in any type of material — thus showcasing the potential for environmentally friendly electronics.

One of the reasons that measuring the orbital Hall effect presents a challenge is that the orbital currents generated do not affect the magnetization of a material directly, so these currents can be detected only indirectly in magnetic materials, through spin–orbit coupling. A possible solution to this problem involves using the light reflected off the surface of a material to measure orbital magnetization through a phenomenon called the magneto-optical Kerr effect. To detect spin accumulation, this experimental technique requires spin–orbit coupling, but if this coupling is weak enough, the measurements are more sensitive to orbital angular momentum than they are to spin.

Choi *et al*. generated accumulations of magnetic moments with different orientations at opposite surfaces of a titanium sample by passing an electric current through it (Fig. 1). They then illuminated the sample with light that was linearly polarized; this means that the light's electric field is confined to a single plane and oscillates along a fixed direction. By analysing the polarization of the beam that was reflected off the surface, they could detect the magnetic moments because the magneto-optical Kerr effect rotates the polarization of light — and the degree of rotation is proportional to the magnetization of the surface. Having confirmed an orbital accumulation resulting from the orbital Hall effect, the authors used complementary measurements to rule out other possible explanations.

Although the data suggest a direct detection of the orbital Hall effect, the measured magnetic-moment accumulation was much smaller than theoretical calculations had predicted[3]. This discrepancy shows that the behaviour of orbital angular momentum in solids is still not fully understood. Estimating magnetic-moment accumulation requires an understanding of how orbital angular momentum diffuses through a material and the different ways in which orbitals can lose their magnetic moment, a process known as relaxation. Although several of these processes are known for spin, little is known about the mechanisms for orbital angular momentum and the interplay between spin and orbital-relaxation processes[5].

Furthermore, other scattering processes that electrons undergo in titanium could potentially lead to orbital relaxation, as well as to other forms of the orbital Hall effect. The presence of impurities in a material with strong spin–orbit coupling can cause electrons to scatter, resulting in a type of spin Hall effect that differs from the one in pure metals. It is unclear whether such scattering processes can also generate an orbital Hall effect.

Choi and colleagues' work and other studies[6] shed light on directions for exploring the potential of orbitronics. One of the most pressing challenges in this field is to understand how orbital dynamics interacts with spins, light and phonons (collective atomic vibrations) — and how these interactions can be used in new technologies. Exploring other orbitronic effects, such as the connection between orbital magnetic moments and electric polarization in solids, could also have far-reaching implications for the future of electronics. But in detecting the orbital Hall effect, Choi *et al*. have taken a key step towards developing methods for manipulating magnetic materials using electric fields alone, eliminating the need for spin–orbit coupling.

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Infection

Viruses trick bystander cells into lowering defences

Timothy M. White & Felicia D. Goodrum

The microenvironment of virus-infected cells and uninfected adjacent cells influences infection. Human cytomegalovirus dampens the immune response of neighbouring uninfected cells, but distant cells can mount an antiviral defence.

The microenvironment around cells is neither simple nor silent. There is a constant chattering of cellular communications that involves membrane-bound proteins, chemical signals such as peptides and even the proteins, lipids and RNAs associated with extracellular vesicles. Cells can therefore talk to themselves, to neighbouring cells and to distant cells. During a viral infection, the conversations between cells take on a warning tone. Writing in *Science Advances*, Song *et al*.[1] shed light on this process.

Signalling molecules called cytokines and interferons, which carry messages through the microenvironment, are released from an infected cell and thereby alert nearby cells to an impending viral threat, enabling them to mount a pre-emptive antiviral defence and limit the spread of infection. These immune signalling pathways are well studied and described for many disease-causing agents. However, viral infection also triggers other less-well-appreciated messages that aid viral objectives. Just as viruses hijack cellular machinery for their own replication, they also disrupt and co-opt communications between cells to thwart antiviral defences in their cellular microenvironment.

Song and colleagues reveal the profound effects of viral infection on neighbouring uninfected cells using human cytomegalovirus (HCMV) as a model system. HCMV belongs to the herpesvirus family and commonly infects humans. Similar to all herpesviruses, it establishes a life-long dormant (latent) infection in an infected individual[2]. Although an HCMV infection does not typically cause overt disease, reactivation of the latent virus

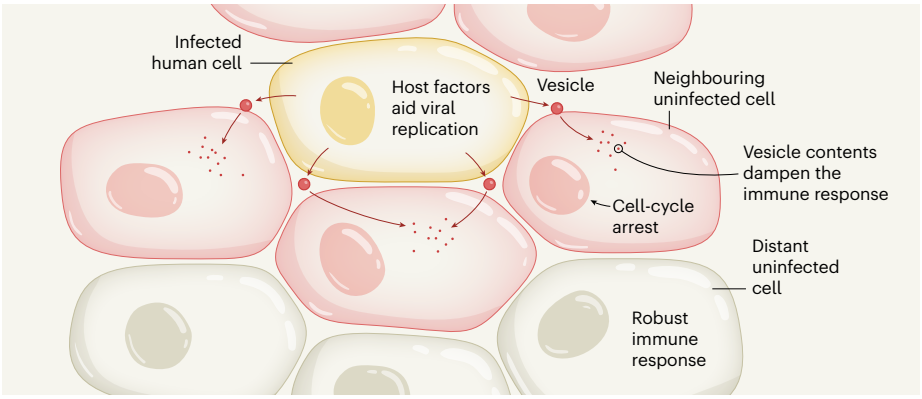

Figure 1 | The complexity of the microenvironment around a human cell infected with a virus. Song *et al.*[1] present protein-expression analysis of three cell populations that were separated for analysis on the basis of their expression profile of engineered fluorescent proteins. Virus-infected host cells fluoresced yellow because they expressed a red fluorescent protein (mCherry) and a green fluorescent protein (GFP) associated with viral infection. These infected cells expressed factors needed for viral replication and released vesicles containing mCherry and factors that hampered the defences of neighbouring uninfected cells. Neighbouring uninfected cells fluoresced red and halted the cell cycle. Uninfected cells distant from the infection site did not fluoresce and expressed proteins indicating a good defensive response.

can be life-threatening in individuals with compromised immune systems. HCMV is also a common cause of congenital disability.

In laboratory studies of infection, most research focuses on the biology of virus-infected cells. Often, studies are carried out using viral inoculations that result in every cell becoming infected. This helps to achieve synchronous infection, allowing the analysis of a temporal sequence of events during infection. Such studies increase the uniformity of the cell population, which would otherwise be reduced by uninfected cells. However, during a viral infection of a human, individual infected cells or small clusters of infected cells are surrounded by mainly uninfected tissue.

What signals do the uninfected cells receive from infected cells, and how do they respond? Using a fluorescent-tagging method, Song and colleagues present work that starts to piece together the complex nature of the virus microenvironment and the altered behaviours of uninfected cells during viral infection (Fig. 1).

The authors engineered a type of human cell called a fibroblast to express a red fluorescent protein (mCherry), and this cell-permeable protein was secreted. They then infected the cells with a virus engineered to express a green fluorescent protein (GFP). Infected, mCherry-secreting cells that appeared yellow, owing to the combination of red and green, were seeded into cultures of unlabelled, uninfected cells. In this co-culture system, cells neighbouring the infected cells took up the secreted mCherry.

Three populations of cells were separated using the system of fluorescent-activated cell sorting. These were the infected cells (yellow), the uninfected neighbouring cells (red) and uninfected distant cells (which did not fluoresce). Each group of cells was then analysed using a method known as mass spectroscopy to determine protein (proteomic) profiles that would distinguish them from a control population of uninfected cells that were not part of this co-culture system.

Remarkably, uninfected cells adjacent to an infected cell had proteomic profiles distinct both from those farther away, and from the infected cells. Even though they did not have viral genomes, uninfected neighbouring cells contained HCMV proteins, indicating that these viral proteins were not derived from a viral infection of the cell. The authors went on to show that these proteins were probably derived from the contents of extracellular vesicles released by infected cells.

"The authors offer an enticing peek into the intricacies of the virus microenvironment."

The proteomic profiles also indicated that neighbouring uninfected cells underwent cell-cycle arrest and had dampened immune responses compared with more-distant uninfected cells. These changes in biological properties depended on the generation and release of extracellular vesicles from infected cells, indicating that signals from infected cells served to prepare their close neighbours for infection.

Song and colleagues show that changes induced by HCMV increased the susceptibility of neighbouring cells to a subsequent infection by influenza or herpes simplex virus, whereas more-distant cells were resistant to infection. These findings are consistent with the proteomic data indicating that the defences of neighbouring cells are dampened by infected cells, whereas distant cells sense infection and mount a defence.

Viral manipulation of uninfected cells has previously been described for hepatitis B virus and enteroviruses, which use RNAs called microRNAs (miRNAs) to disrupt immune responses. These changes result in increased vulnerability of the uninfected cells to viral entry and replication[3–5].

Although the mechanisms for an increased susceptibility to infection are not yet fully understood in the case of HCMV, they probably involve vesicle transport of HCMV-derived interfering miRNAs and of proteins that repress antiviral responses during infection. Further work will be needed to define the relative contributions made to the viral microenvironment by viral proteins and miRNAs, as well as those made by host proteins delivered from infected cells.

Song *et al.* offer an enticing peek into the intricacies of the virus microenvironment. The method for labelling nearby cells was pioneered[6] less than five years ago, and its use in virology is a new development. This work lays the foundation for deeper mechanistic studies to understand the biology behind the viral priming of neighbouring cells for infection and the roles of specific viral proteins and miRNAs. Defining the virus microenvironment will probably help to advance our understanding of herpesvirus latency and reactivation, as well as the resulting cascade of changes that allow sustained viral replication and spread.

The steps leading from a dormant, nearly 'silent' viral genome residing in the nucleus of a cell to the presence of an active infection complete with production of new virus particles remain poorly defined, particularly with respect to the role of the virus microenvironment. Could a reactivating herpesvirus recruit neighbouring cells to bolster its progression from latency to productive infection, and to thereby protect itself from the host's immune system? Song and colleagues take the first steps towards answering this question.

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