“electron-doped” materials that have electron carriers only (blue circles); and artificial interface systems made up of a single FeSe trilayer grown on top of the SrTiO$_3$ (STO) or BaTiO$_3$ (BTO) substrate (red circles). Like the blue group, the materials in the red group have only electron carriers.

The reason why we can regard bulk FeSe as a high-temperature superconductor is its extremely high superconducting gap ($\Delta$) to the Fermi energy ($E_F$) ratio ($\Delta/E_F \sim 1/3$ for holes and $\sim 1$ for electrons). Such high ratios suggest that the size or spatial extent of Cooper pairs ($q$) is extremely small and comparable with the corresponding interparticle distances $1/k_F$. For instance, in $\langle 3 \rangle$, $k_F q$ is estimated to be between 1 and 4, which is several orders of magnitude smaller than that of all known superconductors. Such a small Cooper pair size is a sign of strong electron pair binding. Consistent with that, there are also reports of “giant superconducting fluctuations” above $T_c$ ($\langle 4 \rangle$), which is a sign of preformed, but not condensed, Cooper pairs. In contrast with these results, the spectroscopic signature of preformed pairs—namely, the existence of a normal-state energy gap—is still lacking.

In addition to the unusually high $T_c$, FeSe also exhibits many other puzzling behaviors. Among them is the lack of correlation between its spontaneously breaking of the crystal’s 90° rotation symmetry and magnetic order (as discussed by Sprau et al.). FeSe can be therefore regarded as one of the oddest FeSe-based high-temperature superconductors.

Gerber et al. performed a synchronized measurement of the photoinduced vibration of the Se anions and the associated energy band shifts. Their main finding is an experimental determination of the so-called deformation potential, the potential felt by the Fe electrons due to the displacements of the Se anions (see the figure). The measured size of the deformation potential result is unexpectedly large, which Gerber et al. attribute to the strong correlation between the FeSe carriers. Such strong coupling is, arguably, very similar to the unusual behavior seen in the red group of materials.

Despite having nearly the same band structure, the $T_c$ of the red group is consistently higher than those of the blue group. A hint of why this is so is the observation of replica bands; each electron band possesses a replica at energy $\sim$100 meV away ($\langle 5 \rangle$). Such phenomenon is attributed to the concurrent excitation of a photoelectron from FeSe and a 100-meV phonon in SrTiO$_3$. That this process has an appreciable probability of occurring implies that the FeSe electrons feel a strong deformation potential owing to the displacement of the oxygen anions in SrTiO$_3$ (see the figure). Such strong coupling is believed to explain why $T_c$ is higher in the red group. These results therefore raise the question of whether the strong electron-phonon coupling seen by Gerber et al. is the reason why small Cooper pairs can form in FeSe despite the strong Coulomb repulsion between carriers.

Sprau et al. determined the normal-state Fermi surface and the superconducting gap accurately. Their results show that the superconducting gap is highly anisotropic under the rotation of the crystal. Such anisotropy is expected for FeSe because the crystal rotation symmetry is already broken far above $T_c$. However, what is unexpected is that the gap size correlates with the probability of electrons being in the Fe 3d$_{yz}$ orbital. This led Sprau et al. to propose “orbital-selected Cooper pairing”—only electrons residing in the Fe 3d$_{yz}$ orbital can form Cooper pairs.

Orbital-selected Cooper pairing is most natural when the pairing is very strong. However, contrary to what is expected for such conditions, the superconducting gap minima always occur on the Fermi surface, a phenomenon that is more natural for weak momentum space pairing.

As a function of electron doping, FeSe is known to exhibit two disconnected superconducting phases ($\langle 6 \rangle$). Does this mean that the superconductivity in bulk FeSe is fundamentally different from that in the blue and red groups? Motivated by all these unusual properties, it is safe to predict that there will be many upcoming studies on why FeSe is such a high-$T_c$ superconductor.

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**NEUROViroLOGY**

**Why are neurons susceptible to Zika virus?**

The Zika viral genome binds to a protein expressed by neural progenitor cells

By Diane E. Griffin

Flaviviruses are plus-strand RNA viruses that cause a variety of human diseases, from encephalomyelitis, hepatitis, and hemorrhagic fever to congenital abnormalities. These pathologies reflect different target tissues for virus infection. Zika virus, a flavivirus, shows a tropism for neural progenitor cells, but a detailed understanding of this tendency for infection is not yet well understood. On page 83 of this issue, Chavali et al. (1) report that a specific region of Zika’s RNA genome binds to an RNA-binding protein called Musashi-1 (MSI1), which is highly expressed in neural progenitor cells. These progenitors are precursors for neurons and astrocytes (2), cells required for cortical development. The interaction between Zika viral RNA and MSI1 may explain why these precursor cells are targets for infection (see the figure).

The flavivirus genome encodes a single polyprotein that is processed after translation to produce the individual viral replicase and virion structural proteins. The two nonprotein-coding ends of the genome, the 5′ untranslated region (UTR) and 3′ UTR, consist of highly structured RNAs that interact with cellular, as well as viral, proteins to regulate translation and synthesis of the viral genomic RNA. Availability of cellular RNA-binding proteins for participation in virus replication depends on baseline expression of the relevant proteins in the particular type of cell infected. The nature and normal role(s) of these available factors may determine not only the ability of the virus to replicate, but also the effect and outcome of virus infection. Flavivirus 3′ UTRs are long (400 to 900 nucleotides), complex, distinct for individual flaviviruses, lack a polyadenylated
Target of infection

Interaction between the Zika virus RNA genome and an RNA-binding protein (MSI1) that is highly expressed in neural progenitor cells may explain why infection leads to fewer neural precursors and microcephaly.

[(poly(A)] tail and have multiple regulatory functions (3, 4). MSI1 binds to the 3’ UTR of Zika viral RNA and promotes its translation into the polyprotein that then facilitates viral replication. In an MSI1-expressing cell, Zika virus competes for available MSI1, decreasing MSII interaction with its normal targets. These targets include messenger RNAs (mRNAs) encoding proteins that promote the expression of microcephalin (MCPH1) and cyclin-dependent kinase 6 (CDK6). MCPH1 is expressed during human fetal brain development, and mutations in the encoding gene can cause microcephaly, a smaller brain size. CDK6 is a serine-threonine kinase that controls the cell division cycle, and thus, cell proliferation. MSI1 also represses the translation of mRNAs encoding the proteins Numb and p21, both of which maintain proliferation of neural precursors and cortical development. Zika virus infection results in production of fewer neural precursors and microcephaly.

A cell-type specific role for the 3’ UTR in regulating translation has previously been described for hepatitis C virus infection of hepatocytes, which suggests that members of Flaviviridae, in addition to Zika virus, may have evolved to use cell-specific RNA-binding proteins (5). The importance of the interaction between MSI1 and the 3’ UTR of Zika virus RNA may explain not only the tropism of the virus for neural progenitor cells, but also the damage to the nervous system that results from dysregulation of cellular function.

Brain development is a highly regulated process with staged expression of neural RNA-binding proteins, including MSI1 and members of the Elav (embryonic lethal abnormal vision) family that bind to the 3’ UTR region of mRNAs and increase their stability (6). Many RNA viruses (such as poliovirus, Japanese encephalitis virus, and rabies virus) invade the central nervous system after initial infection and replication in peripheral cells, with preferential replication in certain types of neurons. However, the mechanisms underlying these tissue and cell specificities are not thoroughly understood. Both species-specific and cell-specific tropism of viruses may be due to differences in availability of specific virus receptors on the surface of cells that are required for binding and entry. However, host factors that restrict virus replication after successful entry—many of which are expressed in response to interferon—have been identified for many RNA viruses (7, 8).

The findings of Chavali et al. demonstrate that another factor influencing tropism is the availability of cellular proteins needed for virus replication, and that this availability depends both on the type and developmental maturity of the cell to be infected. Availability of MSI1 for interaction with the 3’ UTR determines the level of Zika virus replication and identifies RNA-binding proteins as a determinant of cellular tropism for flaviviruses and likely other plus-strand RNA viruses that rely on efficient host cell translation of genomic RNA for productive infection.

In addition, the developmental stage of the neural progenitor cells is a determinant of the level of MSI1 expression and thus, their susceptibility to Zika virus infection. For many RNA viruses, the outcome of neuronal infection is age-dependent, with much more efficient replication in immature neurons than mature neurons (9). Indeed, susceptibility of neural progenitor cells to infections that cause neurodevelopmental abnormalities has been recognized (10). Therefore, it will be interesting to explore the role of neural-specific RNA-binding proteins in the tropism and severity of infection for unrelated neurotropic RNA viruses in addition to other flaviviruses.

Viral use of MSI1 also determines the outcome of infection. MSI1 is a translational enhancer for the mRNAs of several cellular proteins, including MCPH1, a protein important for chromatin condensation during cell division. MCPH1 deficiency and genetic defects in the protein can lead to microcephaly, a rare congenital anomaly. Zika virus is unusual among flaviviruses for its ability to cause microcephaly, but Chavali et al. identified differences between Zika virus strains in the number of binding sites and the presence of candidate MSI1 binding sites. Therefore, this is not the only determinant of Zika virus-induced microcephaly.

Zika virus must be able to cross the placenta to infect the fetus, and this likely requires infection of placental trophotroblasts which, interestingly, like neural progenitor cells, are most susceptible to Zika virus when immature (11). RNA virus polymerases are highly error-prone, which increases the adaptability necessary to provide a continuous pool of variants that facilitate infection at different sites and circumstances of replication in vivo (12). Sequence changes in the flavivirus 3’ UTR are important for adaptation to replication in vertebrate and invertebrate hosts (3) so exploration of the importance of Zika virus 3’ UTR variations for replication in trophotroblasts as well as neural progenitor cells and MSI1 interaction would be of interest.

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