

How RNA editing affects the immune system

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Three University of Colorado Cancer Center researchers are part of a team that recently published a paper offering new insight into how the immune system relates to cancer. Quentin Vicens, Ph.D., Jeffrey Kieft, Ph.D., and Beat Vögeli, Ph.D., are authors on the paper, which looks at how an enzyme called ADAR1 operates in pathways associated with cancer.

"In a cell, ADAR1 edits native RNA—or self-RNA—so that the cell recognizes it as its own. It's a key protection against autoimmune disorders," Kieft says. "But if a virus infects, viral RNA isn't edited by ADAR1, so the cell can recognize that and react. The cell knows it has foreign RNA, and it activates immune responses to fight off that infection."

For their paper published last month in the journal *Nature Communications*, Kieft, Vögeli, Vicens, and the rest of the team—including Parker Nichols, a graduate student in the Structural Biology and Biochemistry program in the CU School of Medicine who works jointly in the Kieft and Vögeli labs—looked at where specifically the ADAR1 binds to RNA to perform the editing process. They already knew a domain of ADAR1 known as Z-alpha binds to a form of RNA called Z-RNA, but they found that Z-alpha ADAR1 can bind to other RNA forms as well.

"The team asked, 'How are all these locations in RNA being recognized by Z-alpha if they supposedly don't form Z-RNA?'" Kieft says. "One of the take-home messages is that other forms of RNA can bind to Z-alpha ADAR1 and can even partially form Z-RNA. That was a surprise because it shows that RNA can form this specific Z structure in places we didn't recognize before."

The team is now proposing a model for how Z-alpha ADAR1 is able to bind to different types of RNA. It's an important finding in [cancer research](#) because of the role of ADAR1 in [cancer](#) regulation. A normally functioning [immune system](#) oftentimes can detect cancerous [cells](#) as being dangerous and then eliminate them, but if there's too much ADAR1 editing happening, a cell could be tamping down the [immune response](#) in an effort to protect itself.

"In a lot of cancers, there is upregulation of ADAR1; it is doing more

than it should," Kieft says. "The excess ADAR1 presumably is leading to more RNA editing than is normal. This is going to misregulate things, affecting specific regions of RNA or types of RNA. The excess editing is going to throw off the normal immune response, but it probably has a lot of other affects in the cell as well. Cancer is a disease where [gene regulation](#) has gone awry, so if an important regulatory pathway like editing by ADAR has gone haywire, that can contribute to the cancer."

Knowing all the targets of ADAR1 in a cell is also a step toward more effective therapies, Kieft says. If researchers understand the pathways, they may be able to find a way to disrupt the overactive editing process and boost the immune response. It's a finding applicable to many other diseases as well—Vögeli says since the paper was published, the researchers have heard from other scientists around the country interested in ADAR1.

"We have gotten a lot of feedback on the paper," he says. "There is a lot of interest in this field right now, and other people are interested in how they could use our structural information."

Vögeli and Vicens are now organizing a meeting focused on ADAR1 function and putting together special issues of the journals *Molecules* and *International Journal of Molecular Sciences*.

Vicens says the research project also illustrates the importance of collaborative work and being open to new directions. "I basically brought a new project and direction to the Kieft lab when I joined," Vicens says. "Both labs were open to supporting it intellectually and financially, and the resultant team effort enabled research that would not otherwise have been done."

More information: Parker J. Nichols et al, Recognition of non-CpG

repeats in Alu and ribosomal RNAs by the Z-RNA binding domain of ADAR1 induces A-Z junctions, *Nature Communications* (2021). [DOI: 10.1038/s41467-021-21039-0](https://doi.org/10.1038/s41467-021-21039-0)

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