



Credit: lvcandy/Getty

role of HDAC3 as a transcriptional repressor.

A machine-learning approach revealed DNA sequences associated with DA-independent and DA-dependent genomic regions bound by HDAC3 that could predict transcriptional outcome. In particular, binding of the co-factor ATF2 was associated with DA-independent sites whereas ATF3 binding was associated with DA-dependent sites. In keeping with this, LPS stimulated the transcription of a DA-independent reporter gene containing the ATF2 motif in the presence of ATF2 and inactive HDAC3, whereas LPS-mediated repression of a DA-dependent reporter gene with

the ATF3 motif required ATF3 and wild-type HDAC3. Transcriptional activation by HDAC3 required the transcription factor p65, which was recruited to DA-independent sites by LPS. Deacetylase-dependent transcriptional repression by HDAC3 required the co-repressors NCoR1 and NCoR2, which were recruited to DA-dependent sites enriched for ATF3 binding.

Thus, HDAC3 can switch between activation and repression of target genes dependent on co-factor recruitment, which can promote or inhibit the inflammatory response to LPS, respectively. Mice with reduced catalytic activity of HDAC3 were more susceptible to a lethal dose of LPS, with higher levels of pro-inflammatory cytokines, whereas mice lacking HDAC3 were protected from LPS toxicity. These opposing roles of HDAC3 will need to be considered in the clinical use of HDAC inhibitors.

Kirsty Minton

ORIGINAL ARTICLE Nguyen, H. C. B. et al. Dichotomous engagement of HDAC3 activity governs inflammatory responses. *Nature* <https://doi.org/10.1038/s41586-020-2576-2> (2020)

attachment (four species), permanent mono-attachment of one male and female (three species), or permanent multi-attachment of one female to more than one male (three species). As a control, they also generated genome sequences for three species of anglerfish that mate through non-attachment.

Comparing MHC gene loci, they found that non-attaching and temporarily attaching anglerfish possess a large number of U-type MHC class I genes (*mhc1u*), multiple *mhc2a* alleles and only a few Z-type MHC class I genes (*mhc1z*), which is typical of teleost fish. Although *mhc2* diversity was maintained in anglerfish that show permanent mono-attachment, these fish showed loss of *mhc1u* genes and expansion of *mhc1z* genes. Notably, anglerfish that permanently attached to more than one mate had no functional *mhc1u* genes and at most only one or two *mhc1z* or *mhc2a* genes.

Analysis of genes encoding components of the adaptive immune system revealed more striking adaptations in Ceratioidei. The genes encoding CD8 were absent from the genomes of all six permanently attaching species, and the three species showing permanent

multiple attachments were predicted to lack functional $\alpha\beta$ T cell receptors. Of note, all ten attaching Ceratioidei species lacked the *aicda* gene, which is necessary for antibody affinity maturation, suggesting that attenuation of antibody responses may facilitate attachment. However, only two of the permanently multi-attaching species (*Haplophryne mollis* and *Photocorynus spiniceps*) showed a complete loss of antibody-mediated immunity. *H. mollis* and *P. spiniceps* also showed pseudogenization of *rag1* and *rag2*, indicating that $\gamma\delta$ T cells do not compensate for their loss of adaptive T cell and B cell responses.

Therefore, the unique mating mode of these deep-sea anglerfish is associated with the loss of key components of the vertebrate adaptive immune system. It will be fascinating to further study the unique immune systems of these fish and how they have evolved to protect against potential pathogens lurking in the deep sea.

Yvonne Bordon

ORIGINAL ARTICLE Swann, J. B. et al. The immunogenetics of sexual parasitism. *Science* <https://doi.org/10.1126/science.aaz9445> (2020)

IN BRIEF

COVID-19

A cocktail of antibodies for COVID-19 therapy

Treatment of infectious disease with single monoclonal antibodies (mAbs) can exert a selective pressure that potentially increases the possibility of mutational escape of the targeted antigen. This risk can be reduced through the combination of multiple mAbs targeting non-overlapping epitopes. In this preprint, Baum et al. show the protective effects of REGN-COV2, a cocktail of two fully humanized mAbs that bind to different regions of the SARS-CoV-2 spike protein. Rhesus macaques and golden hamsters treated with REGN-COV2 have markedly lower levels of detectable sub-genomic viral mRNA in both prophylactic and therapeutic settings. In rhesus macaques, the mRNA decrease is evident in oral and nasopharyngeal swabs, as well as in bronchoalveolar lavage. Combined-phase clinical trials for REGN-COV2 are underway.

ORIGINAL ARTICLE Baum, A. et al. REGN-COV2 antibody cocktail prevents and treats SARS-CoV-2 infection in rhesus macaques and hamsters. Preprint at *bioRxiv* <https://doi.org/10.1101/2020.08.02.233320> (2020)

COVID-19

Spatial resolution of SARS-CoV-2 lung infection

In this preprint, Desai et al. provide a spatial analysis of SARS-CoV-2 infection from autopsies of 24 deceased patients with COVID-19. Intra-pulmonary samples were stratified according to viral load using RNA in situ hybridization. They identified a spectrum of viral load between patients and within the same patient. Patients with high viral load had shorter duration of disease, which correlated with distinct transcriptional profiles, including type I/II interferon pathway genes and genes associated with wound healing. Quantification of immune cell subtypes indicated that M1-type macrophages were more abundant in areas positive for SARS-CoV-2 but showed spatially contrasted immune infiltrations within the same patient. Together, these results highlight the intra-pulmonary heterogeneity of immune responses in infected lungs.

ORIGINAL ARTICLE Desai, N. et al. Temporal and spatial heterogeneity of host response to SARS-CoV-2 pulmonary infection. Preprint at *medRxiv* <https://doi.org/10.1101/2020.07.30.20165241> (2020)

COVID-19

Shared CD8⁺ T cell receptors for SARS-CoV-2

Using a high-throughput approach, Snyder et al. profile clonally expanded SARS-CoV-2-specific CD8⁺ T cells both at the individual level, mapping T cell receptors (TCRs) to 545 predicted HLA class I-binding peptides in 61 acute and convalescent patients with COVID-19, and at the population level, decoding shared COVID-19-associated TCRs in 1,015 patients versus control subjects. In total, this preprint identifies 23,179 unique virus-specific TCRs spanning the entire SARS-CoV-2 proteome. Importantly, HLA haplotypes were found to determine both clonal breadth and depth of an individual's virus-specific CD8⁺ T cell response. By applying a logistic regression classifier, the authors show that publicly shared CD8⁺ TCRs may be used as a potential biomarker of current and past SARS-CoV-2 infection at high specificity and sensitivity.

ORIGINAL ARTICLE Snyder, T. M. et al. Magnitude and dynamics of the T-cell response to SARS-CoV-2 infection at both individual and population levels. Preprint at *medRxiv* <https://doi.org/10.1101/2020.07.31.20165647> (2020)

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The authors declare no competing interests.