VACCINES

Vaccines vs antibiotics

Nature **581**, 94–99 (2020)

Prevalent usage of antibiotics worldwide has resulted in the selection for multidrug-resistant microbes. This scenario makes it increasingly difficult to treat common infectious diseases. In *Nature*, Lewnard and colleagues report on how childhood vaccination reduced the incidence of antibiotic usage in low-to-middle-income countries. Their retrospective study looked at children under 5 years of age who had been vaccinated or not against *Streptococcus pneumoniae* and rotavirus, which are causal agents of acute respiratory infection and diarrhea, respectively. They report that children who were vaccinated have lower odds of requiring antibiotic treatment as compared to unvaccinated children of similar age. Indeed, the authors estimate that between 20 and 25% of the children receiving antibiotics for diarrhea or pneumonia had infections that were attributable to the vaccine-targeted infectious agents. Further, they suggest that universal vaccine coverage against these two infectious agents would prevent 40 million cases of children requiring antibiotic treatment. This study makes another compelling case for the benefits of vaccination. *LAD*

https://doi.org/10.1038/s41590-020-0701-x

COVID-19

Anatomy of a response

Cell https://doi.org/10.1016/j.cell.2020.04.026 (2020)

The host response to the pandemic virus SARS-CoV-2 is still being defined. In *Cell*, tenOever and colleagues describe the SARS-CoV-2 host response and compare it to the responses to related coronaviruses MERS and SARS-CoV-1 and to more common respiratory viruses such as RSV and influenza A. Using cell lines, ex vivo human bronchial epithelium and a permissive ferret model of infection, the authors find that SARS-CoV-2 elicits a transcriptional response that is distinct from the other respiratory viruses examined. SARS-CoV-2 results in weak or absent antiviral type I and type III interferon (IFN) responses but strongly induces the proinflammatory cytokines IL (interleukin)-1β and IL-6, as well as the chemokines CCL2 and CXCL8. Some of the chemokines produced are potent monocyte/macrophage and neutrophil attractants, suggesting that these cells might play important roles in the pathology of COVID-19. Finally, broadly similar patterns of strong inflammatory cytokine and weak IFN expression are seen in human post-mortem lung tissue and serum from COVID-19-positive patients. These findings suggest that antagonizing select proinflammatory cytokines might be beneficial in treating COVID-19 symptoms. *ZF*

https://doi.org/10.1038/s41590-020-0703-8

COVID-19

Immune dysregulation

Cell Host Microbe https://bit.ly/35X1jay (2020)

A subset of patients with COVID-19 that require hospitalization undergo a rapid deterioration accompanied by respiratory failure. In *Cell Host & Microbe*, Koutsoukou and colleagues compare the clinical parameters of patients with COVID-19 and patients hospitalized for bacterial sepsis and, retrospectively, patients infected by the 2009 H1N1 influenza virus. Patients with COVID-19 with severe respiratory failure have distinct immune profiles that contrast with the profiles of patients with bacterial sepsis. In particular, although the patients with COVID-19 have higher numbers of circulating monocytes, they have low numbers of natural killer cells and lymphocytes (including $CD4^+$ and $CD8^+$ T cells and $CD19^+$ B cells). Monocytes from patients with severe COVID-19 disease have sustained expression of the cytokines tumor necrosis factor (TNF) and interleukin-6 (IL-6), suggesting a dysregulation of cytokine production. Additionally, the expression of HLA-DR on monocytes from patients with COVID-19 is decreased relative to that of healthy volunteers; this effect is inversely correlated with IL-6 serum concentrations. The expression of HLA-DR on healthy monocytes decreases following culture with plasma from patients with COVID-19 who have immune dysregulation, an effect that could be partially reversed by the addition of tocilizumab to block IL-6 signaling. Indeed, for a subset of patients with severe COVID-19, tocilizumab treatment increased lymphocyte counts, indicating that some patients may be able to rebound from viral-induced immune paralysis. *LAD*

https://doi.org/10.1038/s41590-020-0702-9

TUMOR IMMUNOLOGY

Devious operator

J. Clin. Invest. **130**, 2570–2586 (2020)

Adaptive resistance of tumors is a major impediment to the efficacy of checkpoint inhibition therapies such as anti-PD-1. In *The Journal of Clinical Investigation*, Hanks and colleagues use several murine cancer models of anti-PD-1 treatment to decipher a new pathway of adaptive resistance. Anti-PD-1 treatment results in activation of $CD8^+$ T cells in the tumor microenviroment; however, this response is transient and the tumors ultimately evade control. T cell activation instead triggers a PD-L1- and interferon-γ-dependent pathway in the tumor cells. This results in tumor-intrinsic activation of the NLRP3 inflammasome that ultimately leads to the production of chemokines responsible for the recruitment of immunosuppressive granulocytic myeloid-derived suppressor cells (PMN-MDSCs) that blunt the anti-tumor $CD8^+$ T cell response. Inhibition of NLRP3 activity increases the efficacy of anti-PD-1 treatment in these murine models. These findings identify several potentially druggable targets that could be investigated to complement anti-PD-1-based immunotherapies. *ZF*

https://doi.org/10.1038/s41590-020-0704-7

Laurie A. Dempsey and Zoltan Fehervari