Inflammatory diseases

Zebrafishing for toxins

Here, Sanmarco et al. describe an integrated systems approach involving zebrafish that can identify environmental factors relevant to inflammatory bowel disease (IBD). Using this platform, they show that a common herbicide, propyzamide, promotes intestinal inflammation by suppressing the anti-inflammatory effects of the aryl hydrocarbon receptor (AHR).

The platform developed by the authors integrates human IBD genetics with high-throughput toxicology and small-molecule screens in a chemically induced (TNBS) zebrafish model of colitis. From the ToxCast database (which collects data on environmental chemicals), they identified 111 chemicals that, when examined in bioassays, induced inflammatory mediators linked to intestinal inflammation. By testing these chemicals in the zebrafish colitis model, they found 4 chemicals that suppressed and 13 that exacerbated intestinal pathology.

Using the results from these zebrafish screens as a training set, the authors adopted a machine learning approach to identify additional chemicals in the ToxCast database that may boost intestinal inflammation. The top 20 additional chemicals they identified by this approach included 11 that are used in agriculture; they selected propyzamide for follow-up studies as it is used on crops, gardens and sports fields to control weeds. Oral administration of propyzamide exacerbated TNBS colitis in zebrafish, but did not induce intestinal inflammation in control animals. The exacerbation of colitis by propyzamide was associated with greater tissue pathology, colonic shortening and weight loss, and an increase in IL-17$^+$CD4$^+$, IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cell subsets in the colon. Propyzamide also induced microbial dysbiosis in the intestine, although further studies suggested that this was not linked to its effects on intestinal inflammation. Instead, RNA-sequencing analysis suggested that propyzamide exacerbates colitis by decreasing the ability of AHR signalling to suppress NF-κB-mediated upregulation of C/EBPβ signalling.

Experiments in mice confirmed that propyzamide inhibits AHR signalling and increases the expression of *Il1b*, *Tnf* and *Il23* in activated dendritic cells in a C/EBPβ-dependent manner. Propyzamide enhancement of C/EBPβ signalling in T cells was shown to enhance their recruitment to the intestine and their differentiation into T helper 1 (T_H1) and T_H17 cells. NF-κB-driven C/EBPβ signalling was shown to promote colitogenic T cell responses in mice, and, importantly, this signalling axis was linked to upregulation of T_H1 and T_H17 cell-associated transcriptional modules in patients with IBD.

The authors suggest that propyzamide may interfere with the ability of endogenous AHR ligands (such as microbial metabolites) to mediate anti-inflammatory signalling. The integrated approach they have developed should be a powerful tool for assessing how other environmental factors affect inflammatory diseases.

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Original article: Sanmarco, L. M. et al. Identification of environmental factors that promote intestinal inflammation. *Nature* https://doi.org/10.1038/s41586-022-05308-6 (2022)

In brief

Antifungal immunity

Fungal lipase dampens DC response

The yeast *Candida albicans* is a stable component of the human microbiota and a common cause of superficial fungal infections (candidiasis). Much less common, but significantly more dangerous, is invasive candidiasis. Basso et al. screened mutant *C.albicans* and identified the lipase Lip2 as a virulence factor in systemic infections. *LIP2*-deficient *C. albicans* induced an exaggerated IL-17 response in mice and was readily cleared, whereas its virulence was restored in mice deficient in IL-17A and IL-17F. Further analysis showed that *LIP2*-deficient *C. albicans* activates dendritic cells (DCs) to release IL-23, which induces IL-17 production by γδT cells. In vitro, palmitic acid, a product of lipase activity, inhibited the activation of DCs by *C. albicans*. The authors propose that Lip2 promotes fungal virulence by increasing the local concentration of immune-modulatory fatty acids that dampen the activation of tissue-resident DCs.

Original article: Basso, P. et al. Deep tissue infection by an invasive human fungal pathogen requires lipid-based suppression of the IL-17 response. *Cell Host Microbe* **30**, 1–13 (2022)

COVID-19

'Prime and spike' induces mucosal immunity and reduces SARS-CoV-2 transmission

COVID-19 vaccines have been hugely successful in preventing severe disease. However, waning of immunity and immune evasion by viral variants mean that boosters will continue to be required. Reporting in *Science*, Mao et al. describe a vaccination strategy, which they call 'prime and spike' (P&S), where immunization with a mRNA-based vaccine is boosted through intranasal administration of unadjuvanted spike protein. In a mouse model of lethal SARS-CoV-2 infection, P&S induced robust tissue-specific immune memory and provided superior protection compared to a traditional mRNA-vaccine prime-boost regimen. Similar results were obtained in Syrian hamsters, where P&S also reduced viral transmission. Moreover, boosting with the heterologous SARS-CoV-1 spike protein resulted in robust responses against both SARS-CoV-1 and -CoV-2, indicating that it may also be suitable for the rapid adaptation to new variants.

Original article: Mao, T. et al. Unadjuvanted intranasal spike vaccine elicits protective mucosal immunity against sarbecoviruses. *Science* https://doi.org/10.1126/science.abo2523 (2022)

Immune ageing

Rejuvenation through checkpoint inhibitors?

Senescent cells are known to promote inflammation and contribute to age-related diseases. Wang et al. show that senescent cells heterogeneously express the immune checkpoint protein PDL1, and that the proportion of PDL1$^+$ senescent cells increases with age. These cells appear to be resistant to T cell surveillance and have a stronger senescence-associated secretory phenotype (SASP) compared to their PDL1$^-$ counterparts. Treatment of aged mice with PD1-targeted antibodies reduced the proportion of these cells in a CD8$^+$ T cell-dependent manner. Moreover, it improved age-related conditions such as hepatic lipidosis and decreased grip strength. In a model of non-alcoholic steatohepatitis (NASH), anti-PD1 treatment showed superior efficacy to the senolytic drug ABT263. These results indicate that selective ablation of PDL1$^+$ senescent cells by immune checkpoint-targeted therapy may be a promising strategy for age-related conditions.

Original article: Wang, T.-W. et al. Blocking PD-L1-PD-1 improves senescence surveillance and ageing phenotypes. *Nature* https://doi.org/10.1038/s41586-022-05388-4 (2022)