Credit: S. Bradbrook/Springer Nature Limited

Profiling of the innate immune cell types present in the KPC-OG and KPL-OG mouse models indicated that cDCs were markedly reduced in number and function in pancreatic tumours compared with in lung tumours. In the later stages of disease, there was a 79-fold reduction of cDC1s in pancreatic tumours compared with in lung tumours, and cDC1s in pancreatic tumours showed reduced expression of co-stimulatory molecules and decreased antigen-presenting capacity. Notably, similar observations were made when comparing cDC density in human PDAC and lung adenocarcinomas tissues.

Treatment of KPC-OG mice with FLT3L (which expands DC populations) in the early stages of PDAC led to increased pancreatic infiltration of cDCs and reduced tumour lesions; this was associated with a decreased T_H17-type response and an increase in T_H1 cell and cytotoxic $CD8^+$ T cell responses in the pancreas. FLT3L treatment alone or in combination with anti-CD40 did not lead to regression of established pancreatic tumours; however, the authors found that a triple combination therapy of FLT3L, anti-CD40 and radiotherapy led to regression of established tumours in most KPPC-OG mice.

These findings suggest that cDC number and function can determine whether adaptive immune responses to tumour neoantigens are protective or detrimental in PDAC. Importantly, targeting cDCs may be crucial for effective therapies for PDAC, a disease that has been notoriously difficult to treat.

Yvonne Bordon

ORIGINAL ARTICLE Hegde, S. et al. Dendritic cell paucity leads to dysfunctional immune surveillance in pancreatic cancer. *Cancer Cell* **37**, 289–307 (2020)
RELATED ARTICLE Wculek, S. K. et al. Dendritic cells in cancer immunology and immunotherapy. *Nat. Rev. Immunol.* **20**, 7–24 (2020)

revealed a stronger response for most genes after the second than the first stimulation, in particular those genes involved in cell division, metabolism, granulocyte differentiation and bacterial clearance. By contrast, expression of some inflammatory gene sets was reduced on secondary stimulation, suggesting that LPS pre-exposure improves both host resistance and prevents overreaction to infection. Importantly, there was considerable overlap in the genes induced by secondary LPS stimulation and LPS-induced OCRs, suggesting that the reactivation is mediated by long-term epigenetic changes in HSCs.

So, does LPS induce epigenetic memory in HSCs through direct Toll-like receptor (TLR) signalling or indirectly through LPS-induced cytokines? Analysis of chimeric mice with TLR4-deficient HSCs showed that LPS induced chromatin changes in both wild-type and TLR4-deficient HSCs but the LPS-induced OCRs were almost completely lost in TLR4-deficient cells, suggesting that TLR signalling has an important role in LPS-induced HSC epigenetic memory.

The finding that many LPS-induced OCRs overlapped with binding sites for transcription factors known to be key for myeloid lineage identity PU.1 and C/EBPβ led the authors to investigate the role of these transcription factors in establishing epigenetic memory. Notably, in mixed bone marrow chimeric mice, C/EBPβ-deficient HSCs showed a dramatic loss of LPS-induced OCRs compared with wild-type HSCs. Moreover, the secondary but not primary gene response to LPS was lost in C/EBPβ-deficient cells, suggesting that C/EBPβ is not required for the transient LPS response but is necessary for enhancing gene expression in response to secondary stimulation.

So, memory of previous infection can be stably retained through epigenetic changes occurring in long-term HSCs and conferring increased responsiveness to secondary challenge.

Lucy Bird

ORIGINAL ARTICLE de Laval, B. et al. C/EBPβ-dependent epigenetic memory induces trained immunity in hematopoietic stem cells. *Cell Stem Cell* https://doi.org/10.1016/j.stem.2020.01.017 (2020)

IN BRIEF

COVID-19

Dysregulation of lung myeloid cells in COVID-19

Acute respiratory distress syndrome (ARDS) and robust cytokine storm are the hallmark of severe COVID-19 cases. Using single-cell RNA sequencing of bronchoalveolar lavage fluid, this preprint study from Liao et al. found that the depletion of tissue-resident alveolar macrophages and the accumulation of monocyte-derived inflammatory macrophages associate with disease severity. Inflammatory macrophages adopted interferon-signalling and monocyte-recruiting chemokine programmes that may drive ARDS. Increased clonal expansion of $CD8^+$ T cells was found in mild cases; this may reflect viral clearance due to the induction of virus-specific cytotoxic T cells, as is seen in influenza virus infection. Overall, these data support therapeutic strategies that target the myeloid cell compartment, such as IL-6 inhibitors, to treat COVID-19-associated inflammation.

ORIGINAL ARTICLE Liao, M. et al. The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing. Preprint at *medRxiv* https://doi.org/10.1101/2020.02.23.20026690 (2020)

COVID-19

Fighting COVID-19 exhausts T cells

Lymphopenia is seen in severe cases of COVID-19, but the functional state of T cells in these patients is not known. Based on the retrospective study of 522 patients with COVID-19 and 40 healthy controls from Wuhan, China, this preprint study found that the age-dependent and clinical severity-dependent reduction in T cell numbers inversely correlates with serum levels of TNF, IL-6 and IL-10. The expression of T cell exhaustion markers (PD1 and TIM3) was assessed in peripheral blood cells from 14 patients with COVID-19 and 3 controls. $CD8^+$ T cells from patients in intensive care units (ICUs) showed increased expression of PD1 compared with patients not in ICUs and healthy controls. This suggests that as disease severity progresses in patients with COVID-19, a concomitant rise in inflammatory cytokine levels may drive the depletion and exhaustion of T cell populations.

ORIGINAL ARTICLE Diao, B. et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Preprint at *medRxiv* https://doi.org/10.1101/2020.02.18.20024364 (2020)

COVID-19

In the eye of the COVID-19 cytokine storm

Not all patients with COVID-19 develop the same symptoms, but the immunological determinants of a poor prognosis are unknown. In this preprint article, Yang, Y et al. followed a cohort of 53 clinically moderate and severe patients; they conducted a multiplex screen for 48 cytokines and correlated these results with lab tests, clinical characteristics and viral loads. They found a marked increase of 14 cytokines in patients with COVID-19 compared with healthy controls. Continuously high levels of three of these cytokines (CXCL10, CCL7 and IL-1 receptor antagonist) were associated with increased viral load, loss of lung function, lung injury and a fatal outcome. These observations offer key insights into the immunopathology of COVID-19 and provide new avenues for prognosis and therapy.

ORIGINAL ARTICLE Yang, Y. et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. Preprint at *medRxiv* https://doi.org/10.1101/2020.03.02.20029975 (2020)

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