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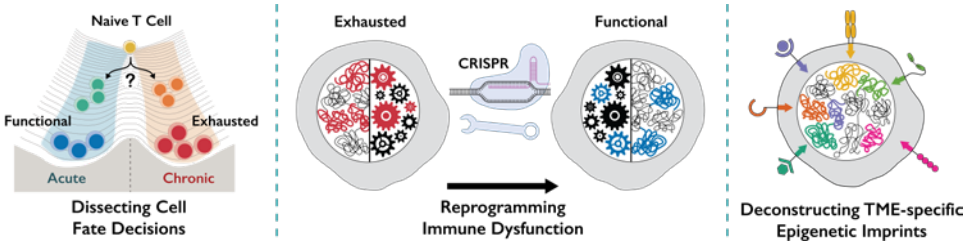
Dysfunction of the immune system is central to disease progression in cancer. **The Sen laboratory** investigates the regulation of T cell dysfunction in tumors and explores epigenetic approaches for T cell engineering. Our work lies at the interface of human immunology, systems biology, and functional epigenomics – merging clinical observations with mechanistic mouse studies to develop novel therapeutic strategies. We have found that the regulatory "circuitry" of dysfunctional T cells differs remarkably from functional T cells fighting off acute viruses. By comparing chronic viral infections and cancer, we demonstrate that this altered epigenetic wiring is a fundamental adaptation to chronic diseases and cannot be rescued by current treatments. Therefore, improved understanding of this altered regulation will be critically important for reversing cancer-associated immune dysfunction. We also pinpoint a radical new approach where we can "tune" specific components of the circuitry in immune cells to remedy their pathological state in cancer while preserving their physiological role in other contexts, thereby minimizing unwanted side-effects in patients.

Effective immunotherapy responses have been limited in 50-70% of patients, in part due to the development of T cell exhaustion wherein CD8+ T cells become dysfunctional and fail to control tumor growth. Despite ongoing clinical efforts to target exhaustion, the fundamental mechanisms specifying this state, and the potential for reinvigorating exhausted T cells, remain poorly understood.

Cell fate and behavior are governed at the level of the epigenome, through transcription factors (TFs) binding to regulatory enhancers. Therefore, we have used the gold-standard mouse model of chronic viral infection to ask whether distinct epigenetic regulation drives CD8+ T cell exhaustion. To overcome technical limitations imposed by low cell numbers, we performed ATAC-seq in exhausted cells and profiled the landscape of accessible chromatin, which is enriched for active enhancers and other regulatory elements. These studies revealed for the first time that exhausted cells acquire an extensive, state-specific epigenetic program that is distinct from memory T cells. We then integrated systems-level characterization of T cell state with CRISPR/Cas9-based enhancer editing in mouse T cell lines to show that these putative enhancers are organized into functional modules and can directly regulate exhaustion-associated genes such as PD-1.

We have sought to translate these findings to other disease contexts. First, by comparison of mouse T cells to those isolated from HCV and HIV chronic infection, we identified a conserved epigenetic program of exhaustion across species. Second, using a mouse melanoma model, we found that tumor-specific CD8+ T cells also share critical epigenetic and transcriptional features with chronic viral infection. Thus, we address a long-standing controversy about how T cell states in cancer relates to chronic viral infection by showing that T cell exhaustion is a fundamental immune adaptation to settings of chronic stimulation. Simultaneously, we have identified epigenetic signatures unique to either disease paradigm, highlighting our ability to define context-specific regulation in an unbiased way.



Leveraging the epigenetic regulation of T cell exhaustion to address fundamental and translational questions: How do T cells commit to exhaustion? How can we rescue exhausted T cells? How do disease-specific tumor microenvironments (TME) shape T cell exhaustion?

Nevertheless, major questions still remain about whether the exhausted epigenetic state is fixed or plastic in response to current treatment modalities. Recently, we examined two of the most prominent therapies to treat chronic infection and cancer: curative anti-viral regimens and immune checkpoint blockade, respectively. In chronic infection, ATAC-seq analysis of HCV-specific CD8+ T cells after cure of viremia did not reverse canonical features of exhaustion, including active super-enhancers near key TFs. In cancer, anti-PD-1 treatment of melanoma tumors also could not rescue the exhausted epigenetic state. T cell exhaustion is therefore an evolutionarily conserved epigenetic state that becomes fixed and is not reversed by some of the most common therapies.

It is becoming evident that alleviating T cell exhaustion will require new targeted approaches to reprogram exhausted cells. Our studies strongly suggest that large-scale epigenetic analysis, paired with precise CRISPR/Cas9 manipulation, will provide a roadmap for rational engineering to prevent T cell exhaustion and improve patient outcomes. To accomplish this, my lab focuses on the following:

1. Dissecting epigenetic mechanisms that govern early differentiation of CD8+ Tcells *in vivo*
2. Defining context-dependent epigenetic map of T cell dysfunction to guide patient therapies
3. Engineering exhaustion-resistant CD8+ T cells through epigenetic manipulation

These projects will generate new insights into the mechanisms and contexts in which T cell exhaustion develops in order to better design patient-specific immunotherapy regimens. In addition, they will enable unprecedented context-specific manipulation of T cell responses and create an integrative framework for characterizing and reprogramming epigenetic regulation of immune dysfunction.

Selected Publications:

Weiss SA, Huang A, Fung ME, Chen C,... Doench JG, Haining WN, Sharpe AH*, **Sen DR**.* Deletion of a state-specific PD-1 enhancer modulates exhausted T cell fate and function. *Nature Immunology* (in revision)

Yates KB, Tonnerre P, Martin GE, Gerdemann U,... Chung RT, Allen TM, Kim AY, Fidler S, Fox J, Frater J, Lauer GM, Haining WN*, **Sen DR***. Epigenetic scars of CD8+ T cell exhaustion persist after cure of chronic infection in humans. *Nature Immunology*. 2021 Aug;22(8): 1020-1029.

Paper was highlighted on the cover of the Aug 2021 issue of Nature Immunology.

Collier JL*, Weiss SA*, Pauken KE, **Sen DR**, Sharpe AH. Not-so-opposite ends of the spectrum: CD8+ T cell dysfunction across chronic infection, cancer, and autoimmunity. *Nature Immunology*. 2021 Jul;22(7):809-819.

Brown FD, **Sen DR**, Godec J, LaFleur MW,... Sharpe AH, Haining WN, Turley SJ. Fibroblastic reticular cells enhance T cell metabolism and survival via epigenetic remodeling. *Nature Immunology.* 2019 Oct 21.

Miller BC*, **Sen DR***, Al-Abosy R, Bi K,... Hodi FS, Rodig SJ, Sharpe AH, Haining WN. Subsets of exhausted CD8+ T cells differentially mediate tumor control and respond to check-point blockade. *Nature Immunology*. 2019 Mar;20(3):326-336.

Sen DR*, Kaminski J*, Barnitz RA, Kurachi M,... Chung RT, Allen TM, Frahm N, Lauer GM, Wherry EJ, Yosef N, Haining WN. The epigenetic landscape of T cell exhaustion. *Science*. 2016 Dec 2;354(6316): 1165-1169.

Paper was highlighted on the cover of the Dec 2016 issue of Science.

*Equal contribution