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How CD4⁺ T-cell help shapes functional and dysfunctional CD8⁺ T-cell differentiation

1. Priming generates a spectrum of CD8⁺ T-cell differentiation states, including terminally differentiated effector cells that have received the most cumulative input from dendritic cells and memory populations that have attained a lower differentiation state. CD4⁺ T-cell help shifts the CD8⁺ T-cell differentiation spectrum in the direction of more effector-like states. – *Restifo & Gatttoni, Curr Opin Immunol, 2013; Henning et al. Nat Rev Immunol, 2018; this thesis.*
2. CD4⁺ T-cell help during priming impacts CD8⁺ T-cell memory by increasing and qualitatively altering the effector memory T cells such that they resemble helped effector CD8⁺ T cells at the transcriptional and epigenetic level. Memory CD8⁺ T cells that have received help during priming, no longer depend on CD4⁺ T-cell help during the secondary response, indicating that CD4⁺ T-cell help improves CD8⁺ T cell-intrinsic memory capacities. – *this thesis.*
3. Stem-like CD8⁺ T cells that are the precursors of exhausted T cells as found in cancer and chronic infections, equal ‘helpless’ cells that have been primed in absence of CD4⁺ T-cell help. – *this thesis.*
4. Stem-like / helpless CD8⁺ T cells lie at the bifurcation point of differentiation towards either functional effector cells or exhausted cells. CD4⁺ T-cell help is required for CD8⁺ T cells to differentiate past the stem-like state towards the CTL effector state. – *Pritykin et al., Mol Cell, 2021; McManus et al., Nature, 2025; this thesis.*
5. The expression of immunogenic helper epitopes by tumor cells does not guarantee that CD4⁺ T-cell help for CTL differentiation is delivered. Lack of Type I interferon signals in the tumor microenvironment may be an important mechanism underlying the lack of CD4⁺ T-cell help delivery to tumor-specific CD8⁺ T cells. – *this thesis.*
6. T-cell priming is a multi-step process. The second priming step by conventional dendritic cell type 1 (cDC1) is not only instrumental for CTL differentiation, but also for the differentiation of precursor CD4⁺ T cells into Th1 cells. – *Borst et al., Nat Rev Immunol, 2018; Lei et al., Nat Commun, 2023; this thesis.*
7. CD4⁺ T-cell depletion in acute or chronic infection models does not allow for a distinction between the direct effects of CD4⁺ T-cell help on CD8⁺ T-cell-intrinsic capabilities and the indirect effects via co-depletion of regulatory T cells or prolonged antigen persistence. – *Li et al., JI, 2015; Zander et al., Immunity, 2019; Jobin et al., Science, 2025; this thesis.*
8. The helpless dysfunction model presented in this thesis provides a new perspective on the mechanism of T-cell priming in cancer. Understanding the role of CD4⁺ T-cell help in CD8⁺ T cell differentiation is crucial for making rational decisions on design or combination of immune therapies. – *this thesis.*
9. ‘The criterion of the scientific status of a theory is its falsifiability (...). It must be possible for an empirical scientific system to be refuted by experience’ – *Karl Popper, the Logic of Scientific Discovery (1959).* As scientists, we should be open to our theories being disproven or modified over time by new experimental evidence, instead of clinging to existing dogmas. Evolving insights are the beauty of science.
10. ‘Als je iets hebt, moet je iets doen’ – *quote by maestro Bas Pollard.* This “first rule of orchestra” also applies to science: If you have something (an interesting finding, a novel idea) you should not wait-and-see, but do something!