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T cell exhaustion is reinforced by progressive De novo DNA methylation programming

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Antigen-specific CD8 T cells play a critical role in controlling chronic infections and cancer, but progressively lose their effector functions during prolonged antigen exposure.Repression of CD8 T cell effector functions, commonly referred to as T cell exhaustion, limits the ability of the immune system to purge the chronic pathogen from the host. It has recently become recognized that CD8 T cell exhaustion programs can be reinforced and heritably maintained. Therefore in order to develop and/or improve current therapeutic approaches that utilize host antigen-specific T cells to treat chronic infections or cancer a major challenge for the field is to identify mechanisms that stabilize T cell exhaustion. We have recently found that epigenetic modifications acquired in pathogen-specific CD8 T cells during prolonged antigen exposure reinforce T cell exhaustion. Using the LCMV model system of chronic viral infection we investigated the role of Dnmt3a mediated de novo DNA methylation in regulating CD8 T cell exhaustion. Strikingly, conditional deletion of Dnmt3a in activated CD8 T cells blocked the cells from becoming exhausted. Longitudinal analysis of whole-genome methylation programming of WT and Dnmt3a cKO CD8 T cells from chronically infected animals reveals progressive acquisition of Dnmt3a-dependent DNA methylation programs in genes, including interferon gamma, that are coupled to the progressive decline of effector functions. These results have significant implications for therapeutic strategies that utilize reactivation of host pathogen-specific CD8 T cells to control chronic viral infections or cancerand provide a nucleotide-resolution map of epigenetic programs progressively acquired during T cell exhaustion.

Biography:

Dr. Benjamin Youngblood, an assistant-member of the Department of Immunology at St Jude Children's Research Hospital, investigates epigenetic mechanisms that regulate the functional impairment of CD8 T cells during chronic viral infections and cancer.Ben received his bachelor of science in Biochemistry from Oregon State University in 2001 and went on to do his graduate training in Biochemistry studying enzyme specificity of DNA methyltransferases at the University of California Santa Barbara. He joined Professor Rafi Ahmed's laboratory in 2007 for postdoctoral training focused on investigating epigenetic regulation of memory CD8 T cell differentiation. In 2014 he joined the faculty at St Jude Children's Research Hospital.