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Indispensable cross-talk between 4-1BB and MyD88 in CD8 T cells mediates costimulatory and anti-tumor effects

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TLR-MyD88 signaling within T cells augments plays a critical role in antitumor responses; MyD88 signaling enhances their survival, facilitates their transition into memory T cells and augments their effector function. In contrast, MyD88 deficiency in T cells results in reduced survival and expansion potential. However, the molecular and cellular mechanisms underlying the prosurvival effects of MyD88 signaling in T cells are poorly understood. Microarray gene analysis data between TLR1-TLR2-stimulated and unstimulated TCR transgenic pmel and MyD88$^{-/-}$pmel CD8 T cells revealed changes in expression levels of several TNF family members. In particular, TLR-MyD88 stimulation increased 4-1BB mRNA and protein levels in pmel and in tumor-specific T cells from melanoma patients. Crosstalk between 4-1BB and MyD88 signaling was highlighted by in fact that: (1) inhibiting 4-1BBL–41BB interaction with neutralizing antibodies hampered the costimulatory effects of TLR1-TLR2 agonist, (2) 4-1BB$^{-/-}$ or 4-1BB$^{-/-}$pmel T cells did not respond to TLR1-TLR2 agonist and (3) MyD88$^{-/-}$ T cells barely responded to 4-1BB stimulation. Furthermore, wild type but not MyD88-deficient mice treated with agonistic anti-4-1BB antibody conjugated to a TLR1-TLR2 agonist increased numbers of tumor–reactive T cells and reversed the growth of an established B16 melanoma tumor. These studies provide novel insights regarding cross-talk between TLR-MyD88–4-1BB signaling in T cells and suggest an approach for enhancing the anticancer efficacy of 4-1BB antibody.

Biography

Eduardo Davila completed his Ph.D from Mayo Clinic Graduate School of Medicine and postdoctoral studies from Mayo Clinic Graduate School. He is an Associate Professor in the Department of Head and Neck Surgery at the University of Maryland, Marlene and Stewart Greenebaum Cancer Center. He has published more than 20 papers in reputed journals and serving as an editorial board member of two journals and on an NIH/NCI study section.

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