J Clin Cell Immunol 2014, 5:5
http://dx.doi.org/10.4172/2155-9899.S1.019

OMICS Group Conferences
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3rd International Conference and Exhibition on
Clinical & Cellular Immunology
September 29-October 01, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Cereblon RING finger E3-ubiquitin ligase receptor is a novel regulator of T-cell activation and homeostasis

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Cereblon (CBBN) is a RING-domain containing protein that likely functions as a substrate receptor for the DDB1/Cul4/CRBN E3 ubiquitin ligase (UbL) complex. Recently, CRBN was shown to be a target of the immunomodulatory (IMiD) drug thalidomide. Although known for inducing severe teratogenicity in the 1950s, this drug class is now used extensively for anticancer immunotherapy. CRBN is expressed in the hematopoietic compartment, but currently has no known function in immune regulation. Ubiquitin ligases including C-Cbl, cbl-b, GRAIL, and ITCH underlie T-cell homeostatic regulation and protect against autoimmunity. To understand the role of CRBN in T-cell function, we studied a mouse with a germline deletion of exon 3 and 4 of this gene. First, crbn-/- mice are viable, fertile and normal in appearance without limb malformations. In the T-cell compartment, splenic and peripheral blood lymphocytes are increased at 3 months of age. The expanded population of splenic T-cells was also evident by immunohistochemical staining. Mature differentiated cell lineages such as CD4 and CD8 single positive (SP) thymocytes, SP peripheral T-cells and naive and memory T-cells are similar to wild-type littermates with no apparent spontaneous autoimmune features at 3 months. Similar to IMiD responses, the mature T-cells from crbn-/- mice showed superior activation after T-cell receptor (TCR) stimulation. Proximal TCR signaling events including pZAP70 and pLck, cytokine production and survival are increased in knockout mice relative to wild-type littermates. In summary, our findings demonstrate a novel role for CRBN, the molecular target of thalidomide and other members of the IMiD-family, in T-cell activation.

Biography

Pearlie Epling-Burnette completed PharmD training at the University of Florida and PhD training at the University of South Florida in 1994. Her Postdoctoral studies were conducted at the H. Lee Moffitt Cancer Center & Research Institute in Tampa, FL. She is now a Senior Member and Professor with Tenure in the Immunology Department at Moffitt Cancer Center and is the author of 74 papers in prestigious medical journals in the field of malignant hematology and immunology.

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A combined *ex vivo* local lymph node assay-BrdU ELISA and irritancy assay to investigate the sensitization and irritancy potential of the chemicals

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In our study to discriminate the sensitization and irritancy potential of the chemicals, the parameters of ex vivo local lymph node assay-BrdU ELISA and irritancy assay were combined. Different concentration of sensitizer and irritant chemicals and a negative control (PABA) were administered on the ears of the Balb/c mice. As parameters of lymph node related assays, the auricular lymph node weights, lymph node cell counts and % change in ear swelling and stimulation index values were calculated. Cytokine releases (IL-2, IFNγ, IL-4, IL-5, IL-1 and TNF-α) from lymph node cell culture were also investigated as endpoints. According to our lymph node related results, the auricular lymph node weights, lymph node cell counts were found to be increased both sensitizers and irritants in high concentrations. On the other hand, according to lymph node cell proliferation results, it was found that there was no 3 fold increase in proliferation of lymph node cells (stimulation index) for irritant chemicals and negative control whereas there was 3 fold increase for sensitizer chemicals in the applied concentrations. Cytokine analyze results indicated that IL-2, IFNγ, IL-4, IL-5 were among the most differentially released cytokines discriminating between irritant contact dermatitisand allergic contact dermatitis.

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