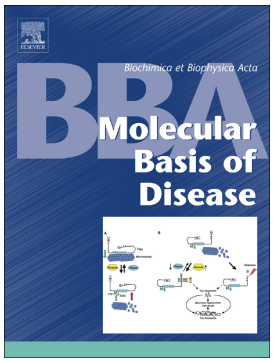

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PII: S0925-4439(17)30340-X
DOI: doi:10.1016/j.bbadis.2017.09.025
Reference: BBADIS 64908

To appear in:

Received date: 26 May 2017
Revised date: 18 September 2017
Accepted date: 25 September 2017

Please cite this article as: Fabienne Gally, Deviyani M. Rao, Carsten Schmitz, Kelley L. Colvin, Michael E. Yeager, Anne-Laure Perraud , The TRPM2 ion channel contributes to cytokine hyperproduction in a mouse model of down syndrome. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Bbadis(2017), doi:10.1016/j.bbadis.2017.09.025

The TRPM2 ion channel contributes to cytokine hyperproduction in a mouse model of Down Syndrome

Fabienne Gally[1, 2], Deviyani M. Rao[1, 2], Carsten Schmitz[1, 2, 3], Kelley L. Colvin[1,4], Michael E. Yeager[1,4], Anne-Laure Perraud[1, 2, 3*]

[1] Linda Crnic Institute for Down Syndrome Research, Colorado, [2] National Jewish Health, Dept. of Biomedical Research,[3] University of Colorado Denver, Dept. of Immunology and Microbiology, [4]University of Colorado Denver, Dept. of Pediatrics, Section of Cardiology, Dept. of Bioengineering

* To whom correspondence should be addressed: Anne-Laure Perraud, PhD Linda Crnic Institute for Down Syndrome Research, National Jewish Health, Dept. of Biomedical Research, 1400 Jackson St., Denver, CO 80206, Tel: (303) 270-2072; E-mail: perrauda@njhealth.org

ABSTRACT

Trisomy 21 (Down Syndrome, DS) is the most common chromosomal anomaly. Although DS is mostly perceived as affecting cognitive abilities and cardiac health, individuals with DS also exhibit dysregulated immune functions. Levels of pro-inflammatory cytokines are increased, but intrinsic alterations of innate immunity are understudied in DS. Furthermore, elevated Reactive Oxygen Species (ROS) are well documented in individuals with DS, further exacerbating inflammatory processes. Chronic inflammation and oxidative stress are often precursors of subsequent tissue destruction and pathologies, which affect a majority of persons with DS.

Together with ROS, the second messenger ion Ca^{2+} plays a central role in immune regulation. TRPM2 (Transient Receptor Potential Melastatin 2) is a Ca^{2+}-permeable ion channel that is activated under conditions of oxidative stress. The Trpm2 gene is located on human Chromosome 21 (Hsa21). TRPM2 is strongly represented in innate immune cells, and numerous studies have documented its role in modulating inflammation. We have previously found that as a result of suboptimal cytokine production, $TRPM2^{-/-}$ mice are highly susceptible to the bacterial pathogen *Listeria monocytogenes* (*Lm*). We therefore used *Lm* infection to trigger and characterize immune responsiveness in the DS mouse model Dp10(yey), and to investigate the potential contribution of TRPM2. In comparison to wildtype (WT), Dp10(yey) mice show an increased resistance against *Lm* infection and higher IFNγ serum concentrations. Using a gene elimination approach, we show that these effects correlate with Trpm2 gene copy number, supporting the notion that Trpm2 might promote hyperinflammation in DS.

Keywords: Transient Receptor Potential Melastatin 2 (TRPM2 ion channel), Listeria, cytokine, Trisomy 21, Down Syndrome, Dp10(yey) mouse