

2nd International Conference on **Endocrinology**

October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

Novel mechanisms of the glucocorticoid receptor in inflammatory bone disease, bone loss and insulin resistance

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Glucocorticoids (GCs) are widely used to treat chronic inflammatory diseases such as rheumatoid (RA) and lead to multiple side effects including GC induced osteoporosis (GIO) and insulin resistance. The current work challenges the dogma that transrepression of pro-inflammatory genes in immune cells by the glucocorticoid receptor (GR) is solely responsible for reducing inflammation, whereas only transactivation of genes liver and bone cells is causing insulin resistance and GIO, respectively. Using conditional and function selective mutant mice for the GR we recently revealed that transactivation of genes by the GR is required to suppress inflammation in mouse models of arthritis *in vivo*. We now surprisingly discovered that in certain arthritis models, GR expression in non-hematopoietic cells suppresses inflammation which challenges the current view that mainly immune cell derived cytokines are the major targets of steroid therapy. Insulin resistance as a GC side effect requires GR dimerization *in vivo* as expected, but surprisingly not its activity in liver cells. In contrast the induction of GIO depends on GR mediated transrepression of genes mainly in bone forming cells, the osteoblasts. By setting up a siRNA screen in pre-osteoblasts we functionally characterized novel GR target genes involved in osteoblast differentiation, which could serve as novel drug targets to avoid GIO. The present work defines new criteria for novel GR modifying compounds and provides new drug targets to optimize steroid therapy.

Biography

Jan Tuckermann has completed his PhD at the age of 29 years from Karlsruhe University, Germany and postdoctoral studies from German Cancer Research Centre, Heidelberg, Germany. After being Group Leader at the Leibniz Institute of Age Research-Fritz Lipmann Institute, Jena, Germany, he is now full professor and director of the Institute of General Zoology at University of Ulm. He has published more than 66 papers in reputed journals and serving as an editorial board member of PLoSOne and International Allergy Drug Targets and reviews numerous journals in the endocrinology, molecular biology, inflammation and bone field.

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