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Novel molecular mechanisms of the glucocorticoid receptor for beneficial and side effects of glucocorticoids

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Glucocorticoids (GCs) are the mainstay of immunosuppressive therapy of acute and chronic inflammation, such as arthritis, despite severe side effects including insulin resistance and osteoporosis. For almost two decades the prevailing view was that side effects of GCs rely on the capacity of the GC receptor (GR), a ligand-induced transcription factor, to dimerize and bind to GC responsive elements on the DNA. In contrast therapeutic anti-inflammatory effects would entirely depend on GR monomer function by interference of the activity of pro-inflammatory transcription factors e.g. NF-kB in immune cells. Based on this dogma pharmaceutical industry developed selective GR ligands that favor GR monomer activities to avoid side effects by maintaining anti-inflammatory efficacies.

We recently challenged this view studying function selective conditional knockout mice for the GR in models of contact allergy, septic shock, arthritis and GC-induced osteoporosis. Surprisingly GR dimerization is required for anti-inflammatory actions of GCs, whereas GR monomer sufficesto cause GC-induced osteoporosis. Recent results on the mechanism of GR in insulin resistance will be discussed.We now identified GR target genes by expression profiling and siRNA screens conferring anti-inflammatory functions and effects on bone.

Our work defines new criteria of properties of GR ligands that are successful in avoiding bone loss and favors anti-inflammatory and unravels novel drug targets mediating specific GR actions.

Biography

Jan Tuckermann studied Biology and performed his graduate studies in the labs of Peter Herrlich (Karlsruhe, Germany) and Peter Angel (Heidelberg, Germany) and his postdoc with Günther Schütz (Heidelberg, Germany). He then worked as a group leader in at the Fritz Lipmann Institute (Jena, Germany) and was 2012 appointed as a full Professor to Head the Institute of General Zoology and Endocrinology at the University of Ulm (Germany). He made major contribution to the molecular mechanisms of corticosteroids in beneficial and side effects of steroid therapy and published 65 peer-reviewed papers. He serves as a board member at PLoSONE, IADTT.

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