Unravelling how glucocorticoids work in rheumatoid arthritis

Hardy, Rowan; Cooper, Mark S.

DOI:
10.1136/annrheumdis-2017-212762

Document Version
Peer reviewed version

Citation for published version (Harvard):
Hardy, R & Cooper, MS 2018, 'Unravelling how glucocorticoids work in rheumatoid arthritis', *Nature Reviews Rheumatology*, pp. 1759-4804. https://doi.org/10.1136/annrheumdis-2017-212762

Unravelling how glucocorticoids work in Rheumatoid Arthritis

Rowan Hardy[1] and Mark S Cooper[2]

1.~~,~~ Institute for Metabolism and Systems Research, University of Birmingham, Birmingham, UK

2. ANZAC Research Institute, Concord Clinical School, University of Sydney, Sydney, NSW, 2139

Using mice with targeted deletion of the glucocorticoid receptor (GR) Koenen et al.[1] recently examined the cell types mediating the anti-arthritic effects of therapeutic glucocorticoids. In the serum transfer induced arthritis (STIA) model, rather than targeting immune cells they found that glucocorticoids exerted their effects through cells of the stromal compartment. This work highlights that despite being available for almost 70 years we are only now beginning to understand a medication that remains essential in the treatment of rheumatoid arthritis (RA).

A range of elegant in vivo approaches were used to determine how glucocorticoids reduced joint inflammation. Bone marrow chimeras (generated by irradiating mice to destroy immune cells and then using donor cells to repopulate the marrow) and inducible genetic deletion of the GR (using a tamoxifen inducible Cre-Lox system) allowed mice to be generated with selective deletion of GR in either the haematopoietic or stromal compartment. The absence of the GR in haematopoietic cells had no impact on the ability of dexamethasone to suppress joint swelling and inflammation. However, absence of the GR in the stromal compartment rendered mice unresponsive to glucocorticoid effects on joint inflammation.

This work follows on from the authors' earlier work in an alternative mouse model of joint inflammation termed adjuvant induced arthritis (AIA).[2] Interestingly in AIA mice they found that the anti-inflammatory effects of glucocorticoids were completely dependent on the presence of the GR in T cells, where IL-17 and Th17 cell suppression appeared to be major targets. Here, ~~T~~there appeared to be no contribution from GR present in the stroma. The situation is further complicated in other inflammatory models, which suggest GR within macrophages are critical to the actions of glucocorticoids.[3] ~~This~~These findings highlight that whilst ~~illustrates that in different models of arthritis~~ glucocorticoids have similar therapeutic effects ~~on arthritis~~in different inflammatory models, ~~but that these effects are~~these can be mediated by very different cell types. An unresolved question is how each of these mouse models translates into the clinical situation of RA and related joint diseases.

Although not traditionally thought of as a major target of glucocorticoids the stroma is increasingly implicated as a target of glucocorticoid action in inflammatory arthritis. Mice with deletion of the GR in chondrocytes have exaggerated inflammation in both the AIA and STIA model highlighting a possible anti-inflammatory role for chondrocytic glucocorticoid signalling in arthritis.[4] Somewhat paradoxically glucocorticoid signalling in osteoblasts appears to be pro-inflammatory with blockade of the GR resulting in reduced inflammation in STIA mice.[5] In the paper by Koenen et al. the stromal

cells appear to regulate inflammation ~~through the~~ by polarising ~~recruitment of specific subsets of~~ macrophages ~~with~~ towards a suppressive phenotype characterised by increased efferocytosis and~~increased~~ expression of anti-inflammatory markers. It is not clear how chondrocytes or osteoblasts exert their effects on inflammation. These results collectively indicate that several stromal cell types (synovial fibroblasts, chondrocytes and osteoblasts) can mediate effects of glucocorticoids on joint inflammation.

An additional level of regulation of glucocorticoid action is the glucocorticoid metabolising enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). This enzyme amplifies glucocorticoid signalling through the local ~~production of active from inactive~~activation of glucocorticoids from inactive precursors. This enzyme is critical to the conversion of inactive glucocorticoids such as cortisone and prednisone to their active counterparts cortisol and prednisolone. Importantly 11β-HSD1 does not metabolise dexamethasone. Mice defective in 11β-HSD1 develop exaggerated joint inflammation in acute and chronic model of arthritis.[6,7] 11β-HSD1 activity within macrophages appears to be critical in restraining inflammation in these models.[8] It would be interesting to know whether the responses seen by Koenen et al. with dexamethasone are similar using glucocorticoids that are regulated by 11β-HSD1 such as those typically used to treat patients with RA.

The novel finding that the stroma can be an important target opens up the prospect of developing medications that have the beneficial anti-inflammatory effects of glucocorticoids without the adverse actions. This long held goal has proven impossible to date. Earlier attempts to develop more selective glucocorticoids (selective glucocorticoid receptor agonists [SEGRAs]) resolved around the notion that the beneficial effects of glucocorticoids were due to the GR interfering with pro-inflammatory signalling pathways as a monomer (termed repression) whereas the adverse effects were due to the GR binding as a dimer to DNA (termed activation).[9] Koenen et al. examined this issue using mice that carried a mutated GR that was unable to form a dimer and as such could only 'repress' and not 'activate'. They found that, whilst the monomer was able to suppress pro-inflammatory cytokines such as TNFα, IL-1β and IFNγ, the ability of the GR to dimerise was essential for the anti-inflammatory effects of glucocorticoids. This finding illustrates that the simplistic view of repression being good and activation bad is not tenable as a basis of developing SEGRAs. So should SEGRAs be developed on the basis of selective targeting of stromal cells? Perhaps tempering enthusiasm for a stromal targeted glucocorticoid like therapy is that the most prominent adverse effects of glucocorticoids such as osteoporosis, osteonecrosis, myopathy and skin thinning are manifested through actions on stromal cells.[10]

A persisting question remains the applicability of these findings to people with RA and related conditions. It is unclear whether the animal models of arthritis individually or collectively mimic the biology seen in the clinic. It is possible that the most important targets of glucocorticoids change during the clinical course of inflammatory arthritis. The models employed so far focus on the short term relieve of joint inflammation by glucocorticoids rather than their long term impact on disease activity and joint integrity. Unfortunately the clever experimental techniques employed on mice by Koenen et al. cannot be used in humans to address the extent to which glucocorticoids target the stroma. What are now needed are novel translational approaches to study the actions of glucocorticoids in patients with RA. Without improved approaches to target glucocorticoids selectively to either the stromal or classical immune cells in patients with inflammatory arthritis it will be difficult to determine the relative contributions of each of these.

Despite their vintage, glucocorticoids continue to give us surprises regarding how they work. This work by Koenen et al. uncovers facets of glucocorticoid action that suggest new options to optimise their effectiveness.

Acknowledgments: None

Competing interests: None

1 Koenen, M. *et al.* Glucocorticoid receptor in stromal cells is essential for glucocorticoid-mediated suppression of inflammation in arthritis. *Ann Rheum Dis*, doi:10.1136/annrheumdis-2017-212762 (2018).
2 Baschant, U. *et al.* Glucocorticoid therapy of antigen-induced arthritis depends on the dimerized glucocorticoid receptor in T cells. *Proceedings of the National Academy of Sciences of the United States of America* **108**, 19317-19322, doi:10.1073/pnas.1105857108 (2011).
3 Tuckermann, J. P. *et al.* Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy. *J Clin Invest* **117**, 1381-1390, doi:10.1172/JCI28034 (2007).
4 Tu, J. *et al.* Endogenous glucocorticoid signaling in chondrocytes attenuates joint inflammation and damage. *FASEB J* **32**, 478-487, doi:10.1096/fj.201700659R (2018).
5 Buttgereit, F. *et al.* Transgenic disruption of glucocorticoid signaling in mature osteoblasts and osteocytes attenuates K/BxN mouse serum-induced arthritis in vivo. *Arthritis Rheum.* **60**, 1998-2007 (2009).
6 Coutinho, A. E. *et al.* 11β-HSD type 1, but not type 2, deficiency worsens acute inflammation and experimental arthritis in mice. *Endocrinology* **153**, 234-240 (2012).
7 Hardy, R. S. *et al.* 11 Beta-hydroxysteroid dehydrogenase type 1 regulates synovitis, joint destruction, and systemic bone loss in chronic polyarthritis. *Journal of autoimmunity* **92**, 104-113, doi:10.1016/j.jaut.2018.05.010 (2018).
8 Zhang, Z. *et al.* Macrophage 11beta-HSD-1 deficiency promotes inflammatory angiogenesis. *The Journal of endocrinology* **234**, 291-299, doi:10.1530/JOE-17-0223 (2017).
9 Cooper, M. S., Zhou, H. & Seibel, M. J. Selective glucocorticoid receptor agonists: glucocorticoid therapy with no regrets? *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* **27**, 2238-2241, doi:10.1002/jbmr.1753 (2012).
10 Hardy, R. S., Zhou, H., Seibel, M. J. & Cooper, M. S. Glucocorticoids and bone: consequences of endogenous and exogenous excess and replacement therapy. *Endocrine reviews*, doi:10.1210/er.2018-00097 (2018).

J Clin Invest. 2007 May;117(5):1381-90. Epub 2007 Apr 19.

Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy.