EC Pharmacology and Toxicology Editor's Column - 2017

Two Faces of Glucocorticoid Receptor (GR) Signaling

Morshedul Alam
Tohoku University
Japan

COLUMN ARTICLE

Glucocorticoids (GCs), a steroid hormone, are cholesterol-derived hormones secreted by the zona fasciculata of the adrenal glands and in human they are known as cortisol. They regulate a variety of physiological functions and also maintain stress-related homeostasis. GC signals through glucocorticoid receptor (GR), which is regulated in a stress-regulated manner to sustain various metabolic and homeostatic functions, which are indispensable for life. So that, GCs homeostasis is beneficial to health, which is controlled by the hypothalamic-pituitary-adrenal axis at the circulatory level, whereas their tissue levels are controlled by enzymes such as 11 β-HSD1 that regenerate and activate GCs [1].

Now a day, glucocorticoids are the most effective therapy for the treatment of inflammatory diseases such as asthma, allergic rhinitis, ulcerative colitis, rheumatoid arthritis, and eczema as well. Although GR signaling makes a critical contribution to the maintenance of systemic energy homeostasis, excessive activation of GR signaling by increased GC levels also possesses several adverse side effects in biological system and that would be life threatening such as diabetes, hypertension, glaucoma, muscle atrophy, growth retardation, and cardiovascular dysfunction. Beside these, Cushing's disease is a characteristic disorder of hyperglucocorticoidism [2]. Especially in liver, GCs have been implicated in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [3]. Mice deficient in 11 β-HSD1, which regenerates GC and amplifies local GC action, are protected from hepatic steatosis induced by excessive GC administered in drinking water, suggesting that appropriate regulation of GC turnover in tissues is critical for the prevention of NAFLD and NASH. Indeed, 11 β-HSD1 inhibitors have been shown to effectively improve metabolic syndrome parameters in rodents [4], and in a clinical trial, liver fat were modestly but significantly decreased in NAFLD patients after treatment with an 11 β-HSD1 inhibitor [5].

Recent data suggests that excessive GR signaling would have adverse effect to aging associated disorders. It has been reported that GR signaling suppresses antioxidant response by regulating the master antioxidant gene regulator, NRF2. NRF2 is a transcriptional activator mediating inducible expression of antioxidant genes under oxidative or electrophilic stress. NRF2 plays important role in response to intrinsic oxidative stress. ROS elimination capacities are limited in Nrf2-null mice [6] and Nrf2-null mice tend to spontaneously develop various inflammatory disorders, including multi-organ autoimmune inflammation, glomerulonephritis, and immune-mediated hemolytic anemia [7]. The chronic accumulation of intracellular ROS seems to be the causative agent of these disorders. NRF2 also plays an important role in abatement of inflammation via suppressing pro-inflammatory cytokine genes [8]; and it also protects liver from NASH [9].

It was reported that NRF2-dependent antioxidant response

Citation: Morshedul Alam. "Two Faces of Glucocorticoid Receptor (GR) Signaling". EC Pharmacology and Toxicology ECO.01 (2017): 22-24.

was suppressed upon cortisone treatment to the 11β-HSD1 (11 β –hydroxysteroid dehydrogenase 1, which regenerates GC and amplifies local GC action) overexpressed hepatic H4IIE cells, which was reversed by 11β-HSD1 inhibitions, suggesting that elevated level of GR by overactive 11β-HSD1 impairs NRF2-mediated anti-oxidant response [10]. Recently, Alam., et al. has established the molecular mechanism of GR-mediated transrepression effect on NRF2-dependent antioxidant response [11]. They showed that GC-induced GR interacts with the transactivation domain (Neh4/5) of NRF2 and recruited to the antioxidant binding element (ARE) by competing with CBP for the same binding domain followed by reduced enhancer histone acetylation, not promoter histone acetylation and increased histone deacetylation. As a consequence, relaxed chromatins for antioxidant genes are no longer in abundance for transcription leading to GR-mediated transrepression of NRF2 target genes. These effects were not limited to Dexamethasone (Dex) but also Betamethasone (Bet). Another group has also investigated GR-dependent suppression of NRF2 target genes by using clobetasol propionate (CP), another GC, and in this case they showed that CP prevented nuclear accumulation of NRF2 and β-TrCP-dependent degradation of NRF2 [12]. These studies suggested that NRF2-dependent antioxidant response is suppressed by GR signaling either through GR-Neh4/5-domain of NRF2 interaction that leads decreased histone acetylation or NRF2 degradation in a β-TrCP-dependent manner. As it is well known that activation of NRF2 is essential for the prevention of aging associated disorders, so that, excessive GR-signaling would be one of the pathological concern for aging science.

Beside these, in cancer cells, constitutive activation of NRF2 is frequently observed. Highly activated NRF2 target genes, encoding detoxification and antioxidant enzymes, govern a great advantage to cancer cells for survival against anti-cancer drugs and irradiation [13]. Constitutively stabilized NRF2 also promotes cell proliferation, as increased NRF2 activity lowers intracellular ROS level [14] and also redirects glucose and glutamine into anabolic pathways to promote metabolic activities [15]. On the other hand, in normal host cells, increased NRF2 activity confers protection from oxidative stress-induced cell death as well as prevention of cancer metastasis [16]. GR signaling enhances the cell apoptosis and Alam., *et al*. established that excessive GR signaling represses NRF2 antioxidant activity. Regarding the treatment of cancer malignancy, GR agonists would be expected to suppress the increased NRF2 activity in cancer. In contrast, NRF2-dependent antioxidant response will be suppressed by using GR agonists in normal host cells, which is the concern of severe side effects of GR signaling. Thus, a drug delivery method of GR agonists would need to be developed for the inhibition of NRF2 activity in cancer cells, which would be delivered preferentially to the target cancer cells.

BIBLIOGRAPHY

1. Mueller KM., *et al*. "Hepatic growth hormone and glucocorticoid receptor signaling in body growth, steatosis and metabolic liver cancer development". *Molecular and Cellular Endocrinology* 361.1-2 (2012): 1-11.

2. Kadmiel M. *et al*. "Glucocorticoid receptor signaling in health and disease". *Trends in Pharmacological Sciences* 34.9 (2013): 518-530.

3. Du WW., *et al*. "Inhibition of dexamethasone-induced fatty liver development by reducing miR-17-5p levels". *Molecular Therapy* 23.7 (2015): 1222-1233.

4. Prasad SSS., *et al*. "Carbenoxolone treatment ameliorated metabolic syndrome in WNIN/Ob obese rats, but induced severe fat loss and glucose intolerance in lean rats". *PLoS One* 7.12 (2012): e50216.

5. Stefan N., *et al*. "Inhibition of 11β-HSD1 with RO5093151 for non-alcoholic fatty liver disease: a multicentre, randomised, double-blind, placebo-controlled trial". *Lancet Diabetes and Endocrinology* 2.5 (2014): 406-416.

6. Hirayama A., *et al*. "EPR imaging of reducing activity in Nrf2 transcriptional factor-deficient mice". *Free Radical Biology and Medicine* 34.10 (2003): 1236-1242.

7. Ma Q., *et al*. "Multiorgan autoimmune inflammation, enhanced lymphoproliferation, and impaired homeostasis of

reactive oxygen species in mice lacking the antioxidant-activated transcription factor Nrf2". *American Journal of Pathology* 168.6 (2006): 1960-1974.

8. Kobayashi EH., *et al*. "Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription". *Nature Communications* 7 (2016): 11624.

9. Goto M., *et al*. "Alcohol dehydrogenase 3 contributes to the protection of liver from nonalcoholic steatohepatitis". *Genes Cells* 20.6 (2015): 464-480.

10. Kratschmar DV., *et al*. "Suppression of the Nrf2-dependent antioxidant response by glucocorticoids and 11β-HSD1-mediated glucocorticoid activation in hepatic cells". *PLoS One* 7.5 (2012): e36774.

11. Alam MM. *et al*. "Glucocorticoid receptor signaling represses the antioxidant response by inhibiting histone acetylation mediated by the transcriptional activator NRF2". *Journal of Biological Chemistry* 292.18 (2017): 7519-7530.

12. Choi EJ., *et al*. "A clinical drug library screen identifies clobetasol propionate as an NRF2 inhibitor with potential therapeutic efficacy in KEAP1 mutant lung cancer". *Oncogene* (2017): 1-11.

13. Mitsuishi Y., *et al*. "Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming". *Cancer Cell* 22.1 (2012): 66-79.

14. DeNicola GM., *et al*. "Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis". *Nature* 475.7354 (2011): 106-109.

15. Mitsuishi Y., *et al*. "The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism". *Frontiers in Oncology* 2 (2012): 200.

16. Motohashi H., *et al*. "Nrf2-Keap1 defines a physiologically important stress response mechanism". *Trends in Molecular Medicine* 10.11 (2004): 549-557.