1441 THE GLUCOCORTICOID RECEPTOR (GR)-DEPENDENT REGULATIONS OF CHRONIC INFLAMMATION AND NRF2 AS EMERGING DRUG TARGETS FOR CANCER THERAPY

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Background Oxidative stress resulting from chronic inflammation in the tumor microenvironment is a major contributing factor to cancer development. Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that plays a key role in cellular defense against oxidative stress suggesting the critical role of NRF2 in tumor survival and growth. Indeed, recent studies have demonstrated that NRF2 activation is not only accumulated in many cancer types but also promotes tumor development and metastasis. Thus, these suggest that inhibition of both chronic inflammation and NRF2 could be a promising therapeutic strategy for cancer. However, NRF2 inhibitors have not yet been clinically developed and are considered as emerging unmet medical needs for cancer therapy.

Methods Interestingly, from the clinical compound library screening, we previously showed that a glucocorticoid analog clobetasol propionate (CP) is the most potent NRF2 inhibitor with strong anti-tumorigenic efficacy in tumors with high NRF2 activity. In the present study, we further investigated the anti-tumorigenic efficacy and molecular mechanisms of CP, which are dependent on glucocorticoid receptor (GR).

Results In both xenograft and immunocompetent syngeneic models, CP strongly inhibited the growth of tumors with high NRF2 activity suggesting that the anti-inflammatory effects of CP also contribute to the inhibition of tumor growth. For the mechanisms, we found that GR regulates NRF2 protein stability via physical interaction with NRF2. GR knockdown accelerated whereas overexpression retarded NRF2 protein degradation. Co-immunoprecipitation assay demonstrated that NRF2 interacts with both GR and β-TrCP in the absence of CP. However, CP treatment reduced the interaction between NRF2-GR without affecting NRF2-β-TrCP interaction. Further, Co-IP using the deletion mutants of GR and NRF2 identified that NRF2-ECH homology 7 domain (Neh7D) and GR-ligand binding domain (GR-LBD) are responsible for their interaction, which is well-supported by the 3D modeling data of protein-protein interactions using AlphaFold. Given that β-TrCP is known to interact with Neh6D adjacent to Neh7D in NRF2, this data suggests that GR binding to NRF2-Neh7D may confer steric hindrance to β-TrCP-dependent degradation of NRF2. Finally, overexpression of Neh7D or GR-LBD to disrupt GR-NRF2 interaction was sufficient to accelerate NRF2 protein degradation.

Conclusions Thus, our data provide a novel molecular mechanism of NRF2 degradation regulated by GR-NRF2 interaction. We are currently investigating GR modulators that are biased to the anti-inflammatory and anti-NRF2 activities without increasing metabolic activities of GR. We propose that targeting the GR-NRF2 axis could be a novel therapeutic strategy to inhibit both NRF2 and chronic inflammation in cancer.

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