NIH Award from the National Heart, Lung, and Blood Institute

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- **Project:** Glucocorticoid Receptor Translational Isoforms in Asthma
- **Start Date:** July 1, 2009
- **Total Award Amount:** $252,857

**How the results of this project will benefit society:**
Glucocorticoids, naturally-produced steroid hormones that inhibit the process of inflammation, are indispensable in the treatment of asthma and other inflammatory diseases although side effects such as hypothalamo-pituitary-adrenal suppression, metabolic syndrome, and osteoporosis limit their use. Our goal is to understand the mechanisms by which the glucocorticoid receptor (GR) mediates cell-specific functions, as this information may be useful in the development of treatments for asthma with improved efficacy/risk ratios.

**The problem the project is trying to solve:**
We have recently discovered that the glucocorticoid receptor (GR) has eight distinct translational isoforms expressed variably in a wide range of cell types. These GR isoforms have profoundly different effects on gene expression. We hypothesize that selective GR translational isoforms mediate distinct sensitivities to glucocorticoid-induced apoptosis and regulate cell-specific inflammatory responses in T cell and dendritic cell subsets that are crucial in asthma. We propose that inflammatory stimuli selectively regulate GR isoforms via translational mechanisms.

**How this project will work:**
To test these hypotheses, we will examine primary T cells and dendritic cells obtained from a murine asthma model, cell lines expressing individual GR isoforms, and bone marrow-derived dendritic cells. Studies in Aim 1 will determine in a murine asthma model the identity and function of GR translational isoforms in helper T cells that are sensitive and regulatory T cells (Tregs) that are resistant to glucocorticoid-induced apoptosis. Our preliminary data indicate that helper T cells express predominantly the proapoptotic GR-A isoform whereas Tregs have predominantly the GR-D isoforms that are incapable of inducing apoptosis in osteoblast and T cell model systems. We will determine the role of selective GR isoforms in T cell subset-specific functions and glucocorticoid sensitivities.

Studies in Aim 2 will determine the identity and function of GR translational isoforms in immature and mature dendritic cells that also have distinct sensitivities to glucocorticoid-induced apoptosis. Our preliminary data indicate that immature dendritic cells switch from the GR-D isoforms to expressing the GR-A isoform after maturation. The role of GR isoforms in distinct glucocorticoid sensitivities of immature (insensitive) and mature (sensitive) dendritic cells and in maturational-stage specific functions will be determined.

Studies in Aim 3 will determine the role of translation machinery in regulating the expression of selective GR isoforms. Our previous studies indicate that the GR translational isoforms are produced from a single species of mRNA via ribosomal leaky scanning and ribosomal shunting. Based on our preliminary results, we will focus on the role of eukaryotic initiation factors in selective expression of GR isoforms. These studies will improve our understanding of the cell-specific actions of GR translational isoforms in asthma. Selective GR isoforms are anticipated to mediate cell-specific sensitivities to glucocorticoids and regulate cell-specific functions. In addition, these studies may provide a basis for the development of anti-inflammatory drugs targeting or altering the expression of selective GR isoforms.

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