P035: Peripheral glucocorticoid metabolism selectively modulates innate immune receptor RIG-I

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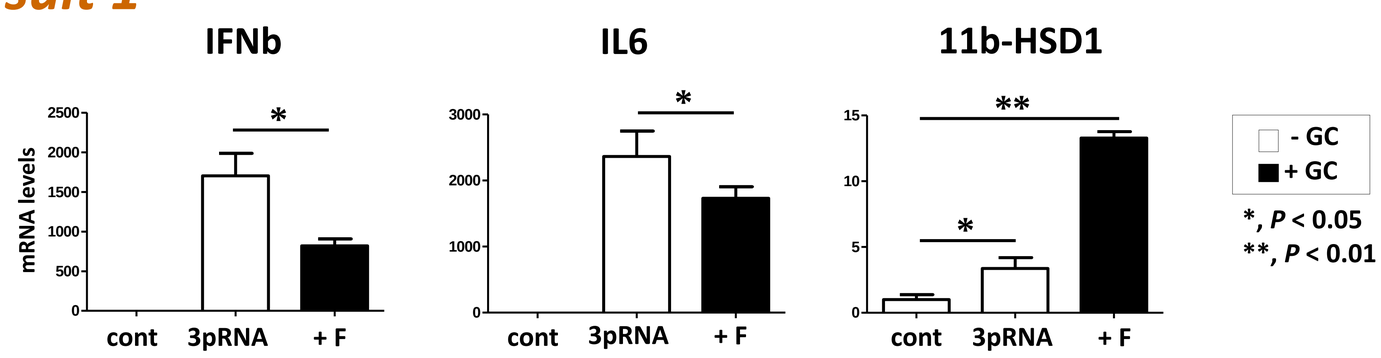
- **Retinoic-acid-inducible gene I (RIG-I) is a cytosolic receptor that sense RNA viruses, such as influenza, producing proinflammatory cytokines (IL6) and type 1 interferons (IFNβ). In severe influenza virus infection, inappropriate immune response can allow influenza virus to proliferate, triggering hypercytokinemia that leads to tissue damage and potentially death of the host.**
- **Glucocorticoid hormones (GC) are clinically used to suppress hypercytokinemia. However, the use of GC is controversial during influenza infection and peripheral GC metabolism remains largely unknown. In peripheral tissues, GC action is controlled by pre-receptor GC metabolizing enzyme 11beta-hydroxysteroid dehydrogenase (11b-HSD). 11b-HSD1 predominantly converts inactive GC to active form within cells. Recent work has shown that 11b-HSD1 modulates immune and inflammatory response.**
- **The aim of this study was to evaluate how peripheral GC metabolism affects RIG-I signaling during influenza infection.**

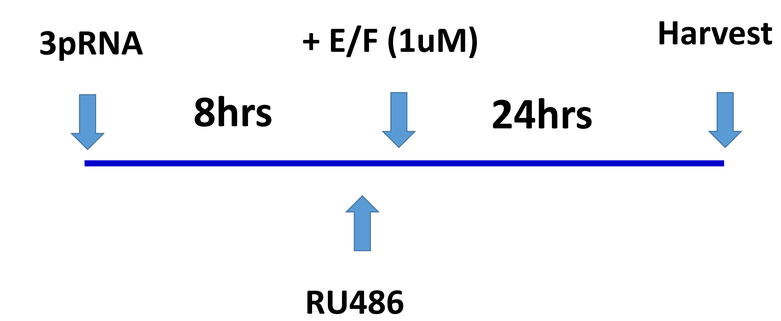
Methods

- **5'-Triphosphate modified RNA (3pRNA), the ligand for RIG-I, was transfected by lipofection in human lung A549 cells. Cells were cultured for 24h in the presence or absence of 1μM glucocorticoids (cortisone/cortisol) following 3pRNA treatment. The glucocorticoid receptor (GR) antagonist, RU486 added 30 min before GC. siRNA was transfected 48h before 3pRNA treatment. Genes were measured by RT-qPCR**

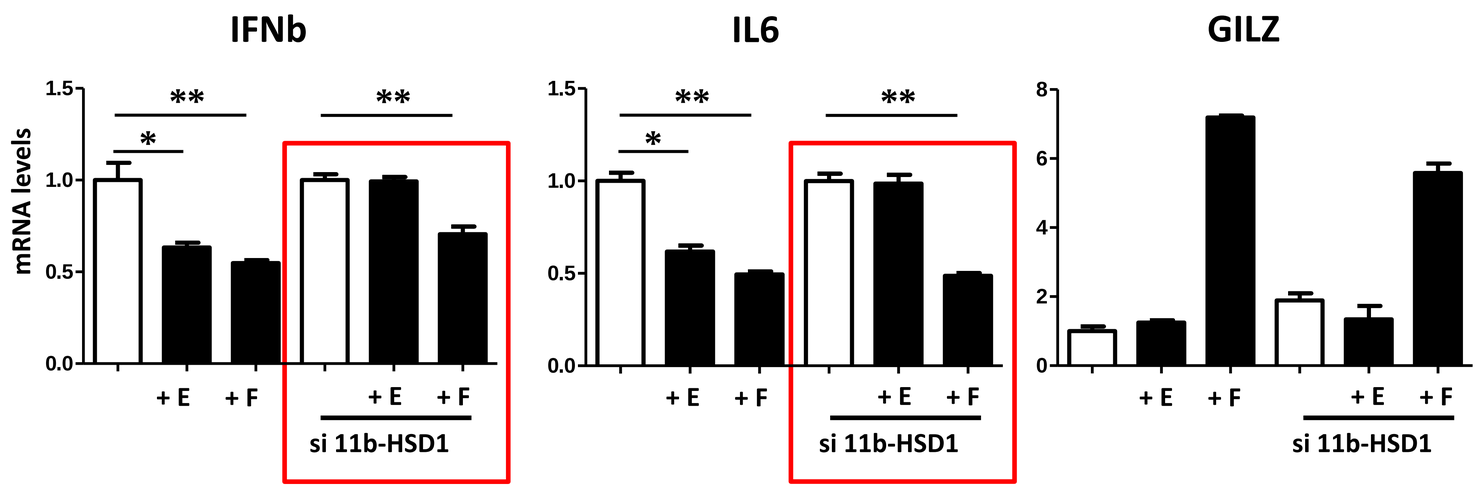
Result 1



- ***Cortisol (F) decreased RIG-I signaling gene levels (IFNb and IL6).***
- ***11b-HSD1 was increased by 3pRNA and further increased by F.***

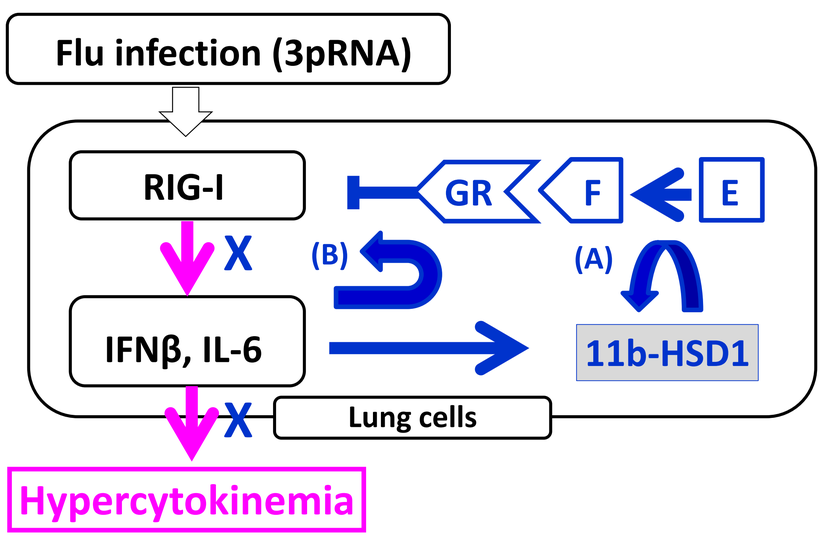


Result 2



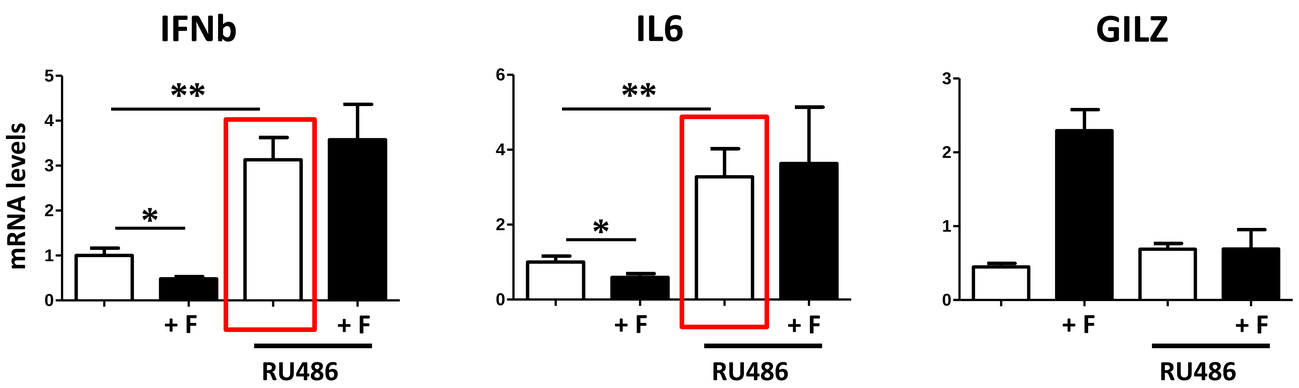
- ***Cortisone (E) and Cortisol (F) suppressed IFNb and IL6 mRNA levels.***
- ***Inhibition of 11b-HSD1 (siRNA) abolished E effects of RIG-I signaling.***
- ***E did not affect GC inducible gene GILZ mRNA levels.***

Hypothesis



11b-HSD1 (A) and GR (B) suppress RIG-I signaling.

Result 3



Inhibition of GR (RU486) induced IFNb and IL6 mRNA levels, suggesting GR could itself suppress RIG-I.

Conclusion

- **Peripheral GC metabolism, 11b-HSD1 and GR, could selectively suppress RIG-I signaling during influenza infection to prevent abnormal cytokine production. Further studies may address the mechanism of hypercytokinemia due to influenza infection.**

This work was supported by JSPS KAKENHI Grant Number JP 16K09792.