Ginseng Pharmacology:

Signaling Pathways of Ginsenoside-Rg1 in Human Umbilical Vein Endothelial Cells

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ABSTRACT

As one of the precious herbs, *Panax ginseng* C.A. Meyer has been used extensively in traditional Chinese medicine for thousands of years and known to be an adaptogen or panacea in resisting a broad spectrum of adverse and stressful conditions. Ginsenosides are the pharmacologically active ingredients in ginseng, from which more than 30 compounds have been identified and characterized. Ginsenoside-Rg1 (Rg1) is one of the most abundant ginsenosides found in ginseng. It is reported that Rg1 possesses angiogenic properties, but the mechanism of action is still elusive.

My study had provided definitive evidence that Rg1 is a functional ligand of the glucocorticoid receptor (GR) as determined by fluorescence polarization assay and other assays conducted on human umbilical vein endothelial cells (HUVEC). Rg1 is also found to increase the phosphorylation of GR, phosphatidylinositol-3 kinase (PI3K), protein kinase B (Akt) and endothelial nitric oxide synthase (eNOS), leading to an increase in nitric oxide (NO) production. Rg1-induced eNOS phosphorylation and NO production were significantly reduced by GR antagonist RU486, PI3K inhibitor LY294002, or Akt inhibitor SH-6. Knockdown of GR completely eliminated the Rg1-induced NO production. The Rg1-induced phosphorylation and the subsequent translocation of the GR to the nucleus were also abolished by RU486. This study revealed that Rg1 can indeed serve as a functional ligand to GR and the activated GR can induce rapid NO production from eNOS via the non-transcriptional PI3K/Akt pathway.

On the other hand, Rg1 can induce an important pro-angiogenic mediator vascular endothelial growth factor (VEGF) expression in HUVEC, which is mediated through PI3K/Akt and TCF/β-catenin-dependent pathway via GR. Rg1 stimulation resulted in an increase in the level of β-catenin, culminating its nuclear accumulation, and subsequent activation of VEGF expression. Transfection of a stable form of β-catenin (S37A), or the use of a glycogen synthase kinase 3β (GSK3β) inhibitor to stabilize β-catenin, induced VEGF synthesis, whereas siRNA-mediated down-regulation of β-catenin did not, confirming that the effect was β-catenin specific. These events are mediated via a PI3K-dependent phosphorylation of the inhibitory Ser-9 residue of GSK3β. In addition, the GR antagonist RU486 was able to inhibit Rg1-induced PI3K/Akt and β-catenin activation.

In summary, my studies provide new insight into mechanisms responsible for part of the Rg1 activities. The Rg1-induced NO and VEGF production in HUVEC confirmed its angiogenic role, which could be clinically important to develop into a new modality for therapeutic angiogenesis.
### TABLE OF CONTENTS

Declaration ........................................... i  
Abstract ............................................. ii  
Acknowledgements .................................. iii  
Table of Contents .................................. iv  
List of Figures ..................................... vii  
List of Tables ....................................... ix  
List of Abbreviations ............................... x  

**CHAPTER 1: Background and Literature Reviews**  
1  
1.1 Ginseng ........................................ 1  
1.1.1 Ginsenosides and its Nomenclatures .......... 4  
1.1.2 Structural Aspect of Ginsenosides .......... 6  
1.1.3 Pharmacokinetic and Bioavailability of Ginsenosides .... 8  
1.2 Cardiovascular System ........................... 11  
1.2.1 Blood Vessels ................................ 11  
1.2.2 Mechanisms of Angiogenesis .................. 13  
1.2.3 Excessive Angiogenesis ....................... 16  
1.2.4 Insufficient Angiogenesis ..................... 17  
1.2.5 Angiotherapy ................................ 17  
1.3 Nuclear Receptors (NR) ........................... 19  
1.3.1 Nuclear Receptor Superfamily ................. 19  
1.3.2 Glucocorticoid Receptor (GR) ................. 21  
1.3.3 GR Subtypes .................................. 22  
1.3.4 Classical Transcriptional Signaling of GR .... 23  
1.3.5 Glucocorticoids (GCs) ......................... 24  
1.3.6 Antagonism to GR ............................. 25  
1.3.7 Co-regulators ................................ 25  
1.4 Aim of the Study ................................ 26  

**CHAPTER 2: Materials and Methods**  
2  
2.1 Ginsenoside-Rg1 .................................. 27  
2.2 Cell Culture ...................................... 27  
2.3 Western Blot Analysis ............................ 27  
2.4 Reverse Transcription-PCR (RT-PCR) ........... 28  
2.5 Confocal Microscopy ............................. 28  
2.6 Transfection Reporter Gene Assay .............. 29
CHAPTER 3: Ginsenoside-Rg1 Induces NO Production

3.1 Introduction

3.1.1 Phosphatidylinositol-3 Kinase (PI3K)/ Protein Kinase B (Akt) Pathway

3.1.2 Endothelial Nitric Oxide Synthase (eNOS)

3.2 Objectives

3.3 Materials and Methods

3.3.1 Experimental Reagents

3.3.2 NO Production Assay

3.4 Results

3.4.1 Rg1 Increases NO Production in Dose- and Time-dependent Manner

3.4.2 Activation of eNOS via the GR and PI3K/Akt Pathway

3.4.3 Rg1 Binds to the GR

3.4.4 Translocation of the Phosphorylated GR

3.5 Discussion

CHAPTER 4: Ginsenoside-Rg1 Induces VEGF Production

4.1 Introduction

4.1.1 Vascular Endothelial Growth Factor (VEGF)

4.1.2 Regulations of VEGF Expression

4.1.3 Glycogen Synthase Kinase 3β (GSK3β)

4.2 Objectives

4.3 Materials and Methods

4.3.1 Experimental Reagents

4.3.2 ELISA

4.3.3 Cell Fractionation

4.4 Results

4.4.1 Rg1 Induces VEGF Production in HUVEC

4.4.2 Rg1-mediated Up-regulation of VEGF Involves Accumulation of β-catenin

4.4.3 β-catenin Stimulates VEGF Expression in a TCF-dependent Manner

4.4.4 Rg1 Induces Phosphorylation of GSK3β in a PI3K-dependent Manner

4.4.5 Rg1 Effects on β-catenin Requires GR

4.5 Discussion
<table>
<thead>
<tr>
<th>CHAPTER 5: Concluding Remarks</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Summary of the Studies</td>
<td>85</td>
</tr>
<tr>
<td>5.2 Further Studies</td>
<td>88</td>
</tr>
<tr>
<td>Appendices</td>
<td>89</td>
</tr>
<tr>
<td>References</td>
<td>99</td>
</tr>
<tr>
<td>List of Publications</td>
<td>114</td>
</tr>
<tr>
<td>Curriculum Vitae</td>
<td>116</td>
</tr>
</tbody>
</table>