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Resource

Electromagnetic field-inducible *in vivo* gene switch for remote spatiotemporal control of gene expression

Junyeop Kim^{1,6}, Yerim Hwang^{1,6}, Sumin Kim¹, Daeyeol Kwon¹, Jeonghyun Park¹, Byounggook Cho¹,
Saemin An¹, Soi Kang¹, Yunkyung Kim¹, Seonghun Kim¹, Christopher J. Lengner², Soochan Kim³,
Youngeun Kwon⁴, Jung-Suk Sung⁵, Jongpil Kim^{1,7}

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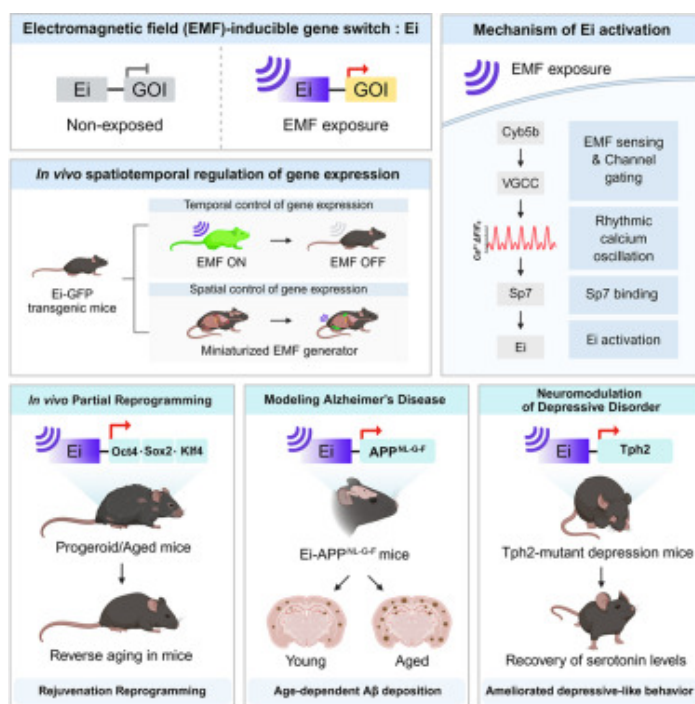
Highlights

- EMF-inducible gene switch (Ei) for precise spatiotemporal gene expression control
- Cyb5b mediates EMF-specific calcium oscillations for gene switch activation
- Ei gene switch enables *in vivo* rejuvenation by reversing aging phenotypes
- Ei system models Alzheimer's disease and restores serotonergic function *in vivo*

Summary

Gaining precise control of gene expression is crucial in biomedical applications. However, spatiotemporal precision remains challenging. Here, we present a remotely controlled *in vivo* gene switch responsive to electromagnetic fields (EMFs) that enables precise spatiotemporal activation of target genes. We uncovered the EMF-inducible gene switch activation mechanism via a CRISPR-Cas9 screen, identifying cytochrome b5 type B (Cyb5b) as an essential mediator likely acting as an EMF sensor. The EMF-inducible gene switch was activated by rhythmic oscillatory calcium dynamics rather than generic calcium influx, defining a precisely tuned and bio-orthogonal induction mechanism. Functionally, EMF activation of the Oct4-Sox2-Klf4 (OSK) cassette induced *in vivo* partial reprogramming in aged mice, conditional expression of human mutant amyloid precursor protein (APP) for Alzheimer's disease (AD) modeling recapitulated pathological features, and EMF-mediated Tph2 expression restored serotonergic activity and ameliorated depressive-like behaviors in Tph2-mutant depression mice. Overall, a remotely controlled EMF-inducible gene switch represents a versatile and effective biomedical platform.

Graphical abstract



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Introduction

Regulatory elements in DNA that control the expression of genes can be co-opted to generate “gene switches” that hold immense potential for both research and therapeutic applications. One such type of gene switch, the “inducible promoter,” can be activated or deactivated by the presence or absence of specific molecules or environmental cues.^{1,2,3} The potential applications of gene switches *in vivo* are vast, particularly in cell and gene therapy, as well as other transgenesis applications. Recently, several types of inducible gene switches have been developed to enable remote control of *in vivo* gene expression using various stimuli such as drugs, light, heat, ultrasound, and electrical signals. For instance, tetracycline-responsive systems enable dose-dependent gene regulation and have been extensively utilized across diverse biological research.⁴ Moreover, optogenetic platforms use light-responsive proteins to precisely control cellular processes, such as channelrhodopsin-mediated regulation of neuronal activity.^{5,6} Similarly, gene switches are responsive to heat, ultrasound, or electricity, leveraging transducers like heat shock protein 70B (HSP70B), Piezo1, or nuclear factor of activated T cells (NFAT) promoters to enable precise *in vivo* regulation for both targeted therapeutics and spatiotemporal studies of gene function.^{7,8,9,10,11} However, current approaches often do not provide precise control over the timing and duration of transgene expression, as they often rely on constitutive promoters or inducible systems that require external stimuli, such as pharmacological agents or light. Moreover, pharmacological agents have off-target effects (or undesirable effects on their endogenous targets), and stimuli such as light are limited in their ability to penetrate target tissues.

Electromagnetic fields (EMFs) are a form of physical energy that describe the interactions between electrically charged particles.¹² Previously, we and others have shown that exposure to precisely defined extremely low-frequency EMFs (EL-EMF) modulates the expression of specific genes involved in stress response, epigenetic remodeling, and cellular signaling pathways in certain cell types with functional outputs ranging from enhanced proliferation, differentiation, cell migration, and epigenetic reprogramming.^{12,13,14,15} Particularly, EL-EMF with direct current (DC) pulsed sine square waveform can effectively penetrate target tissues or areas of the body.¹⁶ Thus, EMF has several advantages as a control for gene switches, including non-invasiveness, precise targeting, and reversibility for *in vivo* application.

In this study, we developed a robust, EMF-responsive gene switch utilizing the leucine-rich repeat-containing G protein-coupled receptor 4 (Lgr4) promoter, which exhibits rapid and reversible activation. Particularly, through a genome-wide CRISPR-Cas9 screen, we identified cytochrome b5 type B (Cyb5b) as a likely EMF sensor, defining the molecular link between electromagnetic inputs and gene regulation. Notably, EMF stimulation triggers distinct, rhythmic Ca^{2+} oscillations, enabling a highly selective and bio-orthogonal mode of gene regulation that provides a non-invasive framework for genetic activation. Next, we explored its application in promoting *in vivo* partial reprogramming. While current approaches utilizing short-term Oct4, Sox2, Klf4, and c-Myc (OSKM) expression show promise in reversing aging, they often risk teratogenesis and hyperplasia due to imprecise regulation.^{17,18,19} Our EMF-inducible system overcomes these limitations by enabling precise spatiotemporal control of cyclic Oct4-Sox2-Klf4 (OSK) expression. Second, we established a

distinct Alzheimer's disease (AD) model that decouples the effects of brain aging from pathogenic A β deposition—a long-standing challenge in traditional models. By accurately recapitulating human-like A β accumulation during aging, our model provides a superior framework for studying AD pathogenesis. Finally, we utilized the system to restore *Tph2* expression in serotonin (5-HT)-deficient R439H *Tph2* knockin (KI) depression mice. By aligning 5-HT synthesis with circadian cycles through rhythmic activation, our platform achieved behavioral recovery, demonstrating its potential for finely tuned, bio-orthogonal neuromodulation. Collectively, these applications highlight the transformative potential of the EMF-inducible gene switch for precise and non-invasive therapeutic interventions across diverse biomedical contexts.

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Section snippets

Development of an EMF-inducible gene switch

To develop an EMF-responsive gene switch, we initially sought to find out genes that could be efficiently stimulated by EMF in the brain. We established an EMF system using a pair of Helmholtz coils (Data S1.1), capable of delivering a magnetic flux density of 0.0–10.0 mT over a 0–200 Hz frequency range. We designed the EMF system to generate unipolar pulsed fields where each 16.67 ms cycle (e.g., 60 Hz) consists of a 5 ms active burst of 20 consecutive single pulses, followed by a 11.67 ms ...

Discussion

In this study, we developed an Ei gene switch that enables precise spatiotemporal regulation of gene expression *in vivo*. Precisely controlled transgene expression *in vivo* via gene switches is becoming increasingly important for the translation of safe and effective gene & cell therapy as well as transgenic technology. Existing gene switches—whether stimulus-responsive (e.g., ultrasound and electrical signals) or drug-inducible—face challenges in precise timing, tissue penetration, and potential ...

Lead contact

Requests for further information and resources should be directed to the lead contact, Jongpil Kim (jpkim153@dongguk.edu ↗). ...

Materials availability

All materials/mouse lines generated in this study are available from the lead contact with a completed materials transfer agreement. ...

Data and code availability

- Raw sequencing data generated in this study (scRNA-seq and bulk RNA-seq) have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject accessions PRJNA1331480 and PRJNA1402770 and are publicly available as of the date of ...

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Acknowledgments

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Author contributions

Junyeop Kim conceptualized the study, developed the methodology, wrote the original draft, reviewed and edited the manuscript, and managed project administration; Y.H. conceptualized the study, developed the methodology, performed investigation and visualization, wrote the original draft, reviewed and edited the manuscript, and managed project administration; S.K. contributed to methodology, investigation, and visualization and performed validation; D.K. developed the software and performed ...

Declaration of interests

The authors declare no competing interests. ...

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
LGR4 antibody	ProteinTech	#20150-1-AP; RRID: AB_2878648 ↗
LGR4 antibody	Invitrogen	#PA5-118812; RRID: AB_2903312 ↗
LGR4 antibody (clone 7E7)	Sigma-Aldrich	#MABS1781; RRID: AB_2855319 ↗
beta-Catenin antibody (D10A8)	Cell Signaling Technology	#8480; RRID: AB_11127855 ↗
beta Actin antibody	Abcam	#ab8227; RRID: AB_2305186 ↗
LEF1 antibody	Abcam	#ab85052; RRID: AB_1861440 ↗
GFP antibody	Abcam	#ab290; RRID: AB_303395 ↗
Tyrosine Hydroxylase antibody	Pel-Freez Biologicals	#p60101-150; RRID: AB_3677426 ↗
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References (45)

I.C. Miller *et al.*
[Remote Control of Mammalian Cells with Heat-Triggered Gene Switches and Photothermal Pulse Trains](#)
ACS Synth. Biol. (2018)

A. Ocampo *et al.*
[In vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming](#)
Cell (2016)

C. Grassi *et al.*
[Effects of 50 Hz electromagnetic fields on voltage-gated Ca²⁺ channels and their role in modulation of neuroendocrine cell proliferation and death](#)
Cell Calcium (2004)

B. Cuccurazzu *et al.*

Exposure to extremely low-frequency (50 Hz) electromagnetic fields enhances adult hippocampal neurogenesis in C57BL/6 mice

Exp. Neurol. (2010)

T. Matsubara *et al.*

BMP2 Regulates Osterix through Msx2 and Runx2 during Osteoblast Differentiation

J. Biol. Chem. (2008)

R.A. Floyd *et al.*

Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases

Neurobiol. Aging (2002)

J.P.Y. Kao *et al.*

Practical aspects of measuring intracellular calcium signals with fluorescent indicators

Methods Cell Biol. (2010)

L. Kaschek *et al.*

Fura-10, unlike fura-2, is suitable for long-term calcium imaging in natural killer (NK) cells without compromising cytotoxicity and can be combined with target cell death analysis

Cell Calcium (2026)

D. Bojar *et al.*

Caffeine-inducible gene switches controlling experimental diabetes

Nat. Commun. (2018)

P. Bai *et al.*

A fully human transgene switch to regulate therapeutic protein production by cooling sensation

Nat. Med. (2019)



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