이현숙

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EDUCATIONS/TRAINING

1990 B.Sc. Ewha Womans University, Dept. of Biology (이화여대 생물학과 이학사)
2000 M.Sc. Seoul National University, Dept. of Biology (서울대학교 생물학과 이학석사)
2004 Ph.D. **University of Cambridge, MRC, Lab of Molecular Biology**
2000-2002. **Wellcome Trust Postdoctoral Fellowship** (Wellcome Trust International Prize. Prof. Frank McKeon. Harvard Medical School & Prof. David Kimelman. Univ. of Washington, Seattle. Dept. of Biochemistry

POSITIONS AND HONORS

2023 ~ Head, **AI-Bio Center**, Seoul National University (서울대학교 AI-Bio 연구단 단장)
2021 ~ 2023. Feb. Dean for Research Affairs of **Seoul National University**/Vice Head of R&D Foundation of Seoul National University (서울대학교 연구처장)
2020– 2021. Visiting Scientist, Health Care Device Team
Samsung Advanced Institute of Technology (SAIT)
2010-2011. Visiting Scientist, **Dana Farber Cancer Institute**, Boston, MA. (Dr. William C. Hahn)
2015 – 2017. Vice Dean of Planning, College of Natural Sciences, **Seoul National University**
2009. Vice Dean of the Faculty of Liberal Education
2020-Present. Board of Trustees, **SUHF** Science Foundation, Korea
2014 – Present. Science Committee & Board of Trustees **KAOS** Foundation
2009-2017. Review Committee of **POSCO** Bessemer Science Fellowship
2011-2016. Committee for **POSCO** Chunggam Science Award
2016-Present: **Editorial Board** member of FEBS J. (Published by European Biochemistry and Molecular Biology Society).

AWARDS [수상]

2014. 마크로젠 여성과학자상
2012. 서울대학교 자연과학대학 연구상
2000. Wellcome Trust International Prize Award (85,000 USD/yr for 2 years)
1997. Cancer Research Campaign Studentship.
1997. Cambirdge Overseas Trust Studentship.
1994. 목암연구소 10 주년 올해의 연구원상

SELECTED PUBLICATIONS

1. Lee S. H., Kwon M. S., Lee T., Hohng S., and Lee H. 2025. Kinesin-like protein KIF18A is required for faithful coordination of chromosome congression with cytokinesis. ***FEBS J***. 10.1111/febs.70019. Feb. 1st. 2025
2. Joo S.Y., Sung K., and Lee H. Balancing act: BRCA2's elaborate management of telomere replication through control of G-quadruplex dynamicity. 2024. ***BioEssays.*** e2300229. https://doi.org/10.1002/bies.202300229

3. Lee J. J., Kim H., Park H., Lee U., Kim C., Lee M., Shin Y., Jung J-J., Lee H-B., Han W., and Lee H. 2023. Disruption of G-quadruplex dynamicity by BRCA2 abrogation instigates phase separation and Break-induced Replication at telomeres 2024. ***Nucleic. Acids Res.*** **52:** 5756-73.
4. Youk J., et al., Lee H., Ju Young Seok. 2024. Quantitative and qualitative mutational impact of ionizing radiation in normal cells. ***Cell Genomics***. 4: 100499.
5. Lee J., Sung K., Joo S.Y., Kim S., Lee H (Co-Corresponding author with Kim S). 2022. Dynamic interaction of BRCA2 with the telomeric G-quadruplex underlies the telomere replication homeostasis. ***Nature Comm***.13: 3396
6. Kim Y., Park J., Joo S. Y., Kim B-G., Jo A., Lee H., Cho Y. 2022. Structure of the human TELO2-TTI1-TTI2 complex. ***J. Mol. Biol***. 434:167370
7. Park J., Yeu S-Y., Paik S., Lee J., Jang J., Lee S., Ko Y-I., Lee H. 2021. Loss of BubR1 acetylation instigates replication stress leading to complex chromosomal rearrangement in tumors. ***FEBS J.*** 288: 5925-5942.
8. Lee J., Lee J., amd Lee H. Alternative paths to telomere elongation. 2021. ***Seminars Cell & Dev. Biol***. invited review. 113: 88-96
9. Park J., Kwon MS., Kim E. E., Lee H., Song E. J. USP35 modulates mitotic progression by modulating the stability of Aurora B. 2018. ***Nature Comm***. 9: 688.
10. Park I., Lee H-O., Choi E., Lee Y-K., Kwon M., Park P-G., Kim J., Kong, Y., Gong G-Y., Lee H. Loss of BubR1 acetylation causes defects in spindle assembly checkpoint signaling and promotes tumor formation. 2013. ***J. Cell Biol***. 202: 295-309. DOI: 10. 1083/jcb.201210099.
11. Choi E., Park P-G., Lee H-O., Lee Y-K., Kang K.H., Lee J.W., Han W., Lee H. C., Noh D-Y., Lekomtsev S., Lee H. (2012). BRCA2 fine-tunes the spindle assembly checkpoint through reinforcement of BubR1 acetylation. ***Dev. Cell.*** 22: 295-308
12. Min J., Hwang K-W., Kim J., and Lee H. (2012). BRCA2 is required for the maintenance of telomere homeostasis. ***J. Biol. Chem***. 287: 5091-5101. (epub ahead Dec. 21. 2011).
13. Choi E., Choi H., Choi, J-Y., Kim J., and Lee H. (2009). BubR1 acetylation at prometaphase is required for modulating APC/C activity and timing in mitosis. ***EMBO J***. **28**: 2077-2089.
14. Lee H., and Kimelman D. (2002). A dominant-negative form of p63 is required for epidermal proliferation in zebrafish. ***Dev. Cell*** 2, 607-616.
15. Lee H., Trainer A. H., Friedman L. S., Thistlethwaite F. C., Evans M. J., Ponder B. A., and Venkitaraman A. R. (1999). Mitotic checkpoint inactivation fosters transformation in cells lacking the breast cancer susceptibility gene, Brca2. ***Mol. Cell*** 4, 1-10.
16. Patel K. J., Yu V. P., Lee H., Corcoran A., Thistlethwaite F. C., Evans M. J., Colledge W. H., Friedman L. S., Ponder B. A., and Venkitaraman A. R. (1998). Involvement of Brca2 in DNA repair. ***Mol. Cell*** **1**, 347-357.

Contributions to Science

1. Identification of the role of BRCA2 tumor suppressor as an essential regulator of DNA repair.

The search for the second Breast cancer susceptibility gene, BRCA2, unrelated to BRCA1 mutation but responsible for half of hereditary cancers of the breast and ovary was sought from 1948. The discovery of *BRCA2* gene, located at Chromosome 13q was isolated from the Icelandic population by the Cambridge group 1995. Sequencing of the gene revealed that BRCA2 gene was a large gene with no homology at all with any known genes, consisted of 27 exons and introns[1]. To reveal the role of the important tumor suppressor BRCA2, genetic knockout in mice was made. In her graduate study, Hyunsook Lee with others in Dr. Ashok Venkitaraman group in MRC, Laboratory of Molecular Biology (LMB) revealed that BRCA2 is involved in error-free double-strand break repair[2]. Then she revealed the molecular basis of chromosome instability in BRCA2-deficient cells: BRCA2-deificient cells require mutation in *p53* or *BubR1* for neoplastic transformation[3].

2. Molecular mechanism of chromosome instability in cancer: Revealing dysfunctional spindle assembly checkpoint (SAC) as the basis of chromosome instability in cancer.

Followed by the identification that mitotic checkpoint inactivation is essential for *BRCA2*-deficient cells to initiate transformation, Lee lab in Seoul National University found that BRCA2 directly regulated the fidelity of chromosome segregation[4]. BRCA2 served as the platform to bring PCAF and BubR1 checkpoint together, where BubR1 K250 was acetylated in prometaphase. Transgenic mice

that were disrupted of the interaction between BRCA2 and BubR1 resulted in the development of chromosome instability-type cancer[5].

3. Discovery of BubR1 acetylation as a novel axis of spindle checkpoint signaling

Acetylation and deacetylation of BubR1 K250 modulated APC/C activity[6]. This work played a key role in establishing the current concept that disassembly of mitotic checkpoint complex (MCC, composed of BubR1, Mad2, Cdc20, Bub3) directs metaphase-anaphase onset, the mitotic exit. Employing knock-in strategy, Lee lab generated acetylation-deficient BubR1 mice (K243R/+) and showed that BubR1 K250 acetylation is crucial for SAC integrity and chromosome-spindle attachment. Furthermore, the mice developed cancers resembling the transgenic mice that were disrupted of BRCA2 and BubR1 interaction, confirming that BubR1 acetylation guarantees chromosome integrity. It also confirmed that BRCA2 is indeed involved in SAC regulation[7].

4. Discovery of telomere G-quadruplex dynamicity in the maintenance of telomere replication homeostasis

Guanine-rich telomere repeat sequences are conserved throughout billion years of Eukaryotic evolution. Arrays of telomere repeats can fold into G-quadruplex (G4) owing to the non-canonical hydrogen bonding between guanines. Lee lab found that telomere G4 performed unique interconversion between two different folded structures during telomere replication. Interconversion between two different conformations is possible through complete unfolding into ssDNA or through partially ssDNA G-triplex (G3) structures. This telomere dynamicity seems to be essential in controlling the access to telomere, therefore is the innate guardian of telomere homeostasis[8]. Intriguingly, BRCA2 binds to G3 and loads RAD51 to the ssDNA to enable the restart of stalled replication forks, as the four-stranded G4 can be a hurdle for replication fork progression. Simultaneously, this remodeling of telomere G4 by BRCA2 prevents the telomere from resection by MRE11, which targets stable G4, in addition to facilitating the restart of stalled forks[8]. This work explains why BRCA2-deficient cells undergo progressive shortening of telomeres[9].

5. Revealing the origin of Alternative Lengthening of Telomeres

The end of chromosomes, telomeres, shorten every time cells divide due to the way DNA replicates. Shortening of telomeres result in replicative senescence, which represents the halt of cell division. Cancer cells overcome senescence and continue to divide by reactivation of telomerase. However, 10-15% of cancers maintain telomeres independent of telomerase, which is termed as Alternative Lengthening of Telomeres (ALT). How cells chose two different mechanisms, telomerase reactivation or ALT during transformation, was not known. Lee lab has shown that the loss of telomere G4 dynamicity, e.g. by the loss of BRCA2 function, results in illegitimate transcription of TERRA (telomere repeat RNA) and R-loop (DNA:RNA hybrid) due to transcription-replication conflict (TRC). Stabilized G4 results in telomere resection, instigating Break-induced Replication (BIR). TERRA-Containing R-loop becomes the seed for phase separation, the dense nucleic acid protein network that facilitates telomere clustering and recombination for ALT[10]. This paper shows that the perturbation of telomere G4 dynamicity is the signal that instigates ALT. Concordantly, BRCA2 deficiency leads to ALT[11].

6. Establishing organoids as a novel platform in studying stem cells and cancer

Lee has shown that p63, a homologue of p53, is the epidermal stem cell factor using zebrafish[12]. Her training with both mouse and zebrafish led her to appreciate the importance developing model organisms to understand human disease. Mouse models have been the favored model system for studying many human diseases including cancer. However, even mouse models had limitations in the analysis of tissues like pancreas, since primary cell culture was not feasible. Lee lab adopted and developed the 3D organoid culture system for studying pancreas cancer from the mouse model the Lee lab developed. After the success from mouse pancreas organoid cultures, Lee lab developed less expensive organoid culture system from the fine-needle biopsy-derived pancreas specimen (patented). Based on this organoid technology, Lee established a start-up Next&Bio that provides the platform for precision medicine, drug screening, and biobanking. Next & Bio was sold to Kolmar Holdings in 2021, a successful example of M&A.