BIOGRAPHICAL SKETCH

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NAME: Henis, Yoav I.

eRA COMMONS USER NAME (credential, e.g., agency login): YHENIS

POSITION TITLE: Professor of Neurobiology, Biochemistry and Biophysics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hebrew University of Jerusalem, Jerusalem, Israel	B.Sc.	10/1974	Chemistry/Biochemistry
Hebrew University of Jerusalem, Jerusalem, Israel	Ph.D.	10/1978	Biochemistry/Biophysics
Washington University Medical School, St. Louis, MO	Postdoctoral	07/1981	Biophysics/Cell Biology

A. Personal Statement

My training and research are in the field of cell membrane biophysics, focusing on signaling by the TGF-β superfamily members (TGF-β, BMPs, GDFs, activins, inhibins) and the interactions between their specific receptors. My studies link molecular interactions of TGF-β superfamily receptors, their membrane and domain organization with their downstream signaling in the context of cancer and other diseases associated with these receptors.

During my postdoc, I have gained expertise in Fluorescence Recovery After Photobleaching (FRAP) studies to measure the lateral diffusion of membrane proteins. Since establishing my own lab, I have continually contributed to this field by the development and application of novel FRAP approaches (patch/FRAP and FRAP beam-size analysis) to measure and analyze quantitatively the dynamics of complex formation between membrane receptors and the membrane interaction dynamics of oncogenic signaling proteins in live cells, as well as the effects of changes in cholesterol-enriched membrane domains (lipid rafts) due to altered levels of cholesterol on these parameters and on signaling. Recently, we have gone also into the field of liquid-liquid phase separation (LLPS) of the central transcription factor TAZ, characterizing the mechanism by which its LLPS condensates are formed in the nucleus and their role in transcription regulation.

1. Rechtman, M.M., Nakaryakov, A., Shapira, K.E., Ehrlich, M. and **Henis, Y.I.** (2009) Different domains regulate homomeric and heteromeric complex formation among type I and type II transforming growth factor-β receptors. J. Biol. Chem. 284, 7843-7852.
2. Marom, B., Heining, E., Knaus, P. and **Henis, Y.I.** (2011) Formation of stable homomeric and transient heteromeric BMP receptor complexes regulates Smad signaling. J. Biol. Chem. 286, 19287-19296.
3. Lu, Y., Wu, T., Gutman, O., Lu, H., Zhou, Q., **Henis, Y.I.**, and Luo, K. (2020) Phase separation of TAZ compartmentalizes the transcription machinery to promote gene expression. Nat. Cell Biol. 22, 453-464.
4. Szilágyi, S.S., Amsalem-Zafran, A.R., Shapira, K.E., Ehrlich, M. and **Henis, Y.I.** (2022) Competition between type I activin and BMP receptors for binding to ACVR2 regulates signaling to distinct Smad pathways. BMC Biol. 20, 50.

B. Positions and Honors

Positions and Employment

1981-1985 Lecturer, Department of Biochemistry, Tel Aviv University, Tel Aviv, Israel

1985-1988 Senior Lecturer (tenured), Department of Biochemistry, Tel Aviv University, Tel Aviv, Israel
1987-1988 Visiting Scientist, Whitehead Institute for Biomedical Research (M.I.T.), Cambridge, MA
1988-1993 Associate Professor, Department of Biochemistry, Tel Aviv University, Tel Aviv, Israel
1992-1993 Visiting Professor, Whitehead Institute for Biomedical Research (M.I.T.), Cambridge, MA
1993-1995 Full Professor, Department of Biochemistry, Tel Aviv University, Tel Aviv, Israel
1995- Full Professor, Department of Neurobiology (formerly Neurobiochemistry), Tel Aviv University, Tel Aviv, Israel
1995-1998 Chair, Department of Neurobiology, Tel Aviv University, Tel Aviv, Israel
1998-1999 Visiting Professor, Whitehead Institute for Biomedical Research (M.I.T.), Cambridge, MA
2003-2004 Visiting Professor, Lawrence Berkeley National Laboratory, Berkeley, CA
2009-2010 Visiting Professor, Duke University Medical Center, Durham, NC
2012-2020 Vice President for Research and Development, Tel Aviv University (term ended 9/2020)

Other Experience and Professional Memberships

1982- Member, Israeli Society for Biochemistry and Molecular Biology
1982- Member, Israeli Society for Cell Biology
1991-1995 Secretary, Israeli Society for Cell Biology
2000-2004 Member, Supreme University Committee for Nominations, Tel Aviv University
2000- Member, American Biophysical Society
2002- Member, American Society for Biochemistry and Molecular Biology (ASBMB)
2003- Member, American Society for Cell Biology (ASCB)
2004- Member, American Society for Microbiology (ASM)
2005-2007 Academic member (Senate representative) of Tel Aviv University Board of Governors
2005-2009 Academic member (Senate representative) of Tel Aviv University Steering Committee
2005-2008 Member, Tel Aviv University Committee for Academic Quality Assessment
2011- Academic member (Senate representative) of Tel Aviv University Board of Governors

Honors

1978 Kennedy-Lee prize for outstanding Ph.D. thesis, Hebrew University, Jerusalem, Israel
1978 Chaim Weizmann Postdoctoral Fellowship (Weizmann Institute, Rehovot, Israel)
1983 Bat-Sheva de Rothschild Fellowship for Distinguished Young Scientists, Jerusalem, Israel
1987 Eleanor Roosevelt Fellowship, the International Union Against Cancer, Geneva, Switzerland
2003- Incumbent of the Zalman Weinberg Chair in Cell Biology, Tel Aviv University
2005 The Jacqueline Seroussi Memorial Foundation Award for Cancer Research, The Jacqueline Seroussi Memorial Foundation, Tel Aviv, Israel

C. Contributions to Science

My major contribution to science is in combining cell biology with membrane biophysics to elucidate the action mechanisms of specific receptors and their interactions, with focus on the TGF-β superfamily receptors. I have initially worked on the mechanism of membrane fusion and endocytosis, and continued into studies on the dynamics, organization and interactions of receptors and signaling proteins involved in cancer (mainly the TGF-β receptors, and oncogenic proteins such as Ras and Src).

1. In the first phase of my scientific career as a PI, I combined FRAP and digital fluorescence microscopy to study the role of viral protein lateral diffusion in membrane fusion. We demonstrated that diffusion of viral envelope proteins is essential for fusion, forming high local density in the membrane contact domains. This elevates the oligomerization of the fusion proteins, enabling perturbation of the adjacent membrane and the cooperative formation of a fusion pore. I have served as the PI in all these studies.
    a. **Henis, Y.I**., Herman-Barhom, Y., Aroeti, B., and Gutman, O. (1989) Lateral mobility of both envelope proteins (F and HN) of Sendai virus in the cell membrane is essential for cell-cell fusion. J. Biol. Chem. 264, 17119-17125.
    b. Aroeti, B., and **Henis, Y.I.** (1991) Accumulation of Sendai virus glycoproteins in cell-cell contact regions and its role in cell fusion. J. Biol. Chem. 266, 15845-15849.

c. Danieli, T., Pelletier, S.L., **Henis, Y.I.**, and White, J.M. (1996) Membrane fusion mediated by the influenza virus hemagglutinin requires the concerted action of at least three hemagglutinin trimers. J. Cell Biol. 133, 559-569.

2. Viruses and cell-surface receptors enter cells by endocytosis. Therefore, we initiated studies on endocytosis through clathrin-coated pits (CCPs). I was the leader of this research project. Initiating the hypothesis that binding of transmembrane proteins to CCPs would affect their lateral diffusion, we employed FRAP-based lateral diffusion studies and fluorescence correlation spectroscopy (FCS) to investigate the endocytosis of gain-of-function mutants of the influenza hemagglutinin (HA) protein. The HA protein itself lacks endocytosis signals and is excluded from CCPs; grafting sequences encoding specific endocytosis signals (short peptide sequences that interact with CCPs) allows direct biophysical assessment of the interactions of each signal with CCPs in live cells. These studies have demonstrated for the first time that membrane proteins can interact transiently with pre-existing CCPs, and that the stability of the interactions depends on the affinity of the specific endocytosis signal. These findings have important implications for the mechanisms of coated pit initiation and of the endocytic sorting of membrane proteins and receptors.
   a. Fire, E., Zwart, D.E., Roth, M.G., and **Henis, Y.I.** (1991) Evidence from lateral mobility studies for dynamic interactions of a mutant influenza hemagglutinin with coated pits. J. Cell Biol. 115, 1585-1594.
   b. Fire, E., Gutman, O., Roth, M.G., and **Henis, Y.I.** (1995) Dynamic or stable interactions of influenza hemagglutinin mutants with coated pits: Dependence on the internalization signal but not on aggregation. J. Biol. Chem. 270, 21075-21082.
   c. Fire, E., Brown, C.M., Roth, M.G., **Henis, Y.I.**, and Petersen, N.O. (1997) Partitioning of proteins into plasma membrane microdomains: Clustering of mutant influenza hemagglutinins into coated pits depends on the strength of the internalization signal. J. Biol. Chem. 272, 29538-29545
   d. Keren, T., Roth, M.G., and **Henis, Y.I.** (2001) Simultaneous binding of internalization-competent influenza hemagglutinin mutants to clathrin-deficient multivalent AP-2 complexes in live cells. J. Biol. Chem. 276, 28356-28363.

3. To study mechanisms involved in cancer development, I have initiated studies (at the role of PI) on the oligomerization of membrane receptors from the TGF-β superfamily and their roles in signaling. Using novel biophysical methods that we have developed to quantify the interactions between receptors at the surface of live cells, we have demonstrated for the first time that both the type I and type II TGF-β superfamily receptors form homodimers, which associate into heteromeric tetramers augmented by ligand binding. We detected a different pattern of oligomerization for TGF-β vs. BMP receptors, which can affect their signaling modes. Recently, we studied activin receptors, and demonstrated that BMP type I receptors can compete with activin type I receptors in binding to a common activin type II receptors, thus providing an important new mechanism for the regulation of signaling between distinct pathways. These findings have important implications for diseases where mutations in receptors from this family are involved. **Henis, Y.I.**, Moustakas, A., Lin, H.Y., and Lodish, H.F. (1994) The types II and III transforming growth factor-ß receptors form homo-oligomers. J. Cell Biol. 126, 139-154.
   a. Gilboa, L., Wells, R.G., Lodish, H.F., and **Henis, Y.I.** (1998) Oligomeric structure of type I and type II TGF-ß receptors: Homo-dimers form in the ER and persist at the plasma membrane. J. Cell Biol. 140, 767-777.
   b. Rechtman, M.M., Nakaryakov, A., Shapira, K.E., Ehrlich, M. and **Henis, Y.I.** (2009) Different domains regulate homomeric and heteromeric complex formation among type I and type II transforming growth factor-ß receptors. J. Biol. Chem. 284, 7843-7852.
   c. Shapira, K.E., Hirschhorn, T., Barzilay, L., Smorodinsky, N.I., **Henis, Y.I.** and Ehrlich, M. (2014) Dab2 inhibits the cholesterol-dependent activation of JNK by TGF-ß. Mol. Biol. Cell 25, 1620-1628.
   d. Marom, B., Heining, E., Knaus, P. and **Henis, Y.I.** (2011) Formation of stable homomeric and transient heteromeric BMP receptor complexes regulates Smad signaling. J. Biol. Chem. 286, 19287-19296.
   e. Szilágyi, S.S., Amsalem-Zafran, A.R., Shapira, K.E., Ehrlich, M. and **Henis, Y.I.** (2022) Competition between type I activin and BMP receptors for binding to ACVR2 regulates signaling to distinct Smad pathways. BMC Biol. 20, 50.

4. The interactions of non-integral oncogenic proteins, such as Ras and Src, with the plasma membrane and with lipid raft domains are crucial for their signaling and their oncogenic potential. As a PI, I have developed a novel biophysical approach based on FRAP beam-size analysis (comparing FRAP with two bleach-beam sizes) to quantify the relative contribution of lateral diffusion and exchange (between membrane and cytosolic pools) to the FRAP dynamics. This provides a measure for the strength and dynamics of the membrane interactions. Our studies on different GFP-Ras isoforms and oncogenic mutants provided the first demonstration that the association of all Ras isoforms with the plasma membrane is relatively stable, and that their affinity to lipid raft domains depends on the Ras isoform and its activation state. We showed that the membrane interactions play a role in Ras signaling *via* specific pathways. Of note, we have shown that external clustering of raft-associated receptors/proteins has strong and distinct on the signaling of each Ras isoform. Analogous studies on the interactions of the oncogenic Src and Fyn proteins with the plasma membrane and lipid rafts showed differential effects, wich depended on their membrane anchorage motifs and interactions with lipid rafts. Importantly, we have recently discovered novel effects of cholesterol reduction by statins (or alternative methods) on TGF-β signaling in epithelial cells downstream of the receptors, which operates via a pathway involving elevated transcription and translation of JNK and c-Jun, enhancing Smad2/3 expression and leading to a much stronger TGF-β mediated formation of pSmad2/3.
    a. Niv, H., Gutman, O., Kloog, Y. and **Henis, Y.I.** (2002) Activated K-Ras and H-Ras display different interactions with saturable nonraft sites at the surface of live cells. J. Cell Biol. 157, 865-872.
    b. Shvartsman, D.E., Donaldson, J.C., Diaz, B., Gutman, O., Martin, G.S. and **Henis, Y.I.** (2006) Src kinase activity and SH2 domain regulate the dynamics of Src association with lipid and protein targets. J. Cell Biol. 178, 675-686.
    c. Eisenberg, S., Beckett, A.J., Prior, I.A., Dekker, F.J., Hedberg, C., Waldmann, H., Ehrlich, M. and **Henis, Y.I.** (2011) Raft protein clustering alters N-Ras membrane interactions and activation pattern. Mol. Cell Biol. 31, 3938-3952.
    d. Shapira, K.E., Ehrlich, M. and **Henis, Y.I.** (2018) Cholesterol depletion enhances TGF-β Smad signaling by increasing c-Jun expression through a PKR-dependent mechanism. Mol. Biol. Cell 29, 2494-2507.

A Complete list of my publications list can be found in PubMed in the following link: https://www.ncbi.nlm.nih.gov/pubmed/?term=Henis+YI