BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Kathleen J. Green	Joseph L. Mayberry Professor of Pathology Professor of Dermatology
eRA COMMONS USER NAME (credential, e.g., agency login) KJGREEN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Pomona College, Claremont, CA.	B.A.	1977	Biology
Washington University, St. Louis, MO.	Ph.D.	1982	Cell, Dev. Biol.
Northwestern Univ. Med. School, Chicago, IL	Post-Doc	1987	Cell, Mol. Biol.

A. Personal Statement: The goal of my laboratory is to elucidate the roles of cadherin adhesion receptors in epithelial tissue morphogenesis, differentiation, inherited disorders and cancer. A particular area of expertise is in defining functions of cell-cell junctions called desmosomes, which anchor intermediate filaments at sites of strong cell-cell adhesion where they are critical for maintaining tissue integrity. Recent studies have revealed unexpected, non-canonical functions of desmosomal proteins as scaffolds that mediate key signaling pathways in differentiation, proliferation and innate immunity in normal and tumor tissue. Loss of the desmosomal cadherin desmoglein 1 occurs early in keratinocytes surrounding melanoma lesions, as well as early stages of non-melanoma tumors. Our work supports the idea that loss of Dsg1 function in melanoma-associated keratinocytes promotes melanoma progression through pro-tumorigenic paracrine signaling. The lab uses vitro, 3D organotypic and in vivo (mouse and human) models of epithelial differentiation and tumor progression to address how these novel functions control tissue development and disease progression.

In the area of administration and education, I serve as Associate Director for Basic Sciences in the R.H. Lurie Comprehensive Cancer Center and in this position I am actively involved in recruitment and in the development of programs that promote basic and translational activities in the cancer center. I am Principle Investigator (PI) and director of a National Cancer Institute-funded T32 in Carcinogenesis that has been the primary source of funding for advanced Ph.D. training in cancer biology at Northwestern for the past 30 years. I also currently serve as Co-Director of the Cancer Biology Cluster of the Northwestern University Life and Biological Sciences Ph.D. Program. I have also served on a number of mentoring committees for junior investigators at Northwestern and outside of the institution.

B. Positions and Honors.

Positions

1987-1993 Asst. Prof., Dept. of Pathology, Northwestern University, Chicago, IL
1993-1997 Assoc. Prof., Depts. of Pathology and Derm., Northwestern University, Chicago, IL
1997-present Prof., Pathology and Dermatology, Northwestern University, Chicago, IL
2009-present Director/Co-Director, Northwestern University Skin Disease Research Center Keratinocyte Core
2014-current Associate Director for Basic Sciences, RH Lurie Comprehensive Cancer Center

Honors

1977 Phi Beta Kappa
1988-1991 March of Dimes Basil O'Connor Award
1990-1993 Am. Cancer Soc. Junior Faculty Research Award
1992/94 Gordon Research Conference- Intermediate Filaments (Vice-Chair 1992; Chair 1994)
1992-1994 J&J Focused Giving Award
1993-1998 American Cancer Society Faculty Research Award
1999 Fellow of the AAAS
2001 Keith Porter Fellow
2001/03 Gordon Conference on Epithelial Differentiation (Vice-Chair, 2001, Chair, 2003)
2002 William Montagna Lecturer, Society for Investigative Dermatology

2006 Tanioku Kihei Lectureship, Japanese Society for Investigative Dermatology
2011 Distinguished Woman in Medicine and Science-Northwestern University (2011)
2012 Martin and Gertrude Walder Award for Research Excellence
2014 Faculty Engagement Award-The Graduate School
2015 Kligman Frost Leadership Award-The Society for Investigative Dermatology
2015-16 Alexander von Humboldt Research Award
2016 Elected to the German National Academy of Sciences-Leopoldina

Selected Leadership, Peer Review and Editorial (since 2000):

2001-06, 09-11 SID Board of Directors
2004-05 American Society for Cell Biology (ASCB) Program Committee
2002-cur Editor/Deputy Editor in Chief- Journal of Cell Science
2002-cur Associate Editor- Journal of Investigative Dermatology
2007-10 National Institute of Arthritis, Musculoskeletal and Skin Disease Advisory Council.
2010 President -Society for Investigative Dermatology
2012-17 Secretary- American Society for Cell Biology- Council

C. Contribution to Science (Total 174 publications; 121 peer-reviewed).

Desmoplakin Structure and Function: Insights into Human Disease: During the early 90's my lab cloned and characterized several core desmosome molecules. Analysis of the one of these, the intermediate filament (IF) anchoring protein desmoplakin, led us to recognize the existence of a gene family, now known as "plakins", members of which have widespread functions in organizing the cytoskeleton. Later, we collaborated with William Weis (Stanford) to determine the high-resolution crystal structure of the desmoplakin intermediate filament (IF) binding domain, the first for an IF-associated protein. These findings provided a foundation for a series of functional studies that provided experimental demonstration for functions of desmoplakin domains and their contributions to tissue integrity. Work from our lab facilitated the identification of the first of many mutations resulting in skin and heart disorders that have been dubbed "Desmoplakinopathies", including severe perinatal lethal skin disease caused by a virtual loss of desmoplakin protein and the sudden death syndrome AC (Arrhythmogenic Cardiomyopathy). In addition to our longstanding work on skin and its diseases, we are members of a Transatlantic Network on cardiac disease supported by the LeDucq Foundation and are actively investigating shared and unique pathogenic mechanisms in skin and heart disease.

1. Bornslaeger, E.A., C.M. Corcoran, T.S. Stappenbeck, and **K.J. Green** (1996). Breaking the connection: Displacement of the desmosomal plaque protein desmoplakin from cell-cell interfaces disrupts anchorage of intermediate filament bundles and alters intercellular junction assembly. *J. Cell Biol.* 134: 985-1002.
2. Choi, H-J, S. Park-Snyder, L.T. Pascoe, **K.J. Green** and W.I. Weis. (2002). Structures of two fragments of the intermediate filament binding protein desmoplakin reveal a unique repeat motif structure. *Nature Struct. Biol.* 9 612-620, pub online July 8, 2002. (*highlighted in. News & Views*).
3. Huen, A.C., J.K. Park, X. Chen, L.M. Godsel, L.J. Bannon, E.V. Amargo, T.Y. Hudson, A.K. Mongiu, I.M. Leigh, D.P. Kelsell, B.M. Gumbiner, and **K.J. Green**. (2002). Intermediate filament-membrane attachments function synergistically with actin-dependent contacts to regulate adhesive strength. *J. Cell Biol.* 159: 1005-1018. (cited in *Faculty 1000*)
4. Dubash, A.D.*, C.Y. Kam*, B. Aguado, D. Patel, M. Delmar, L. Shea and **K.J. Green** (2016). Plakophilin-2 loss promotes TGF-β1/p38 MAPK-dependent fibrotic gene expression in cardiomyocytes. *J. Cell. Biol.* 212: 425-38. PMC4754716. * Equal contribution.

Desmosomal cadherins as signaling scaffolds in epidermal morphogenesis and disease: Our lab was among the first to report that the desmosomal glycoproteins, desmogleins and desmocollins, belong to the cadherin family of adhesion molecules. We showed that in addition to playing a critical role in adhesion, they serve as signaling scaffolds that dictate cell behavior and promote the differentiation of complex tissues. For example, the desmosomal cadherin, desmoglein 1 (Dsg1), attenuates EGFR and MAPK signaling to promote epidermal differentiation by interfering with Ras-Raf coupling through its association with an ERBIN-Shoc2 complex. On the other hand, EGFR elevates desmosomal cadherin turnover in tumor cells to attenuate cadherin signaling

functions and reduce adhesion strength. In collaboration with geneticist Eli Sprecher (Tel Aviv University) we showed that loss of Dsg1 in patients with the skin disorder Striate Palmoplantar Keratoderma (SPPK) have elevated MAPK signaling associated with increased proliferation and loss of differentiation. This work has implications for understanding "RASopathies" associated with cutaneous and hair defects as well as a common malignant skin tumor, basal cell carcinoma. Along with Dr. Sprecher, we showed that loss of membrane-associated Dsg1 results in a severe disorder termed SAM syndrome "Severe dermatitis, multiple Allergies and Metabolic wasting". This disease is associated with loss of cell-cell adhesion and barrier function, but also increased expression of genes encoding allergy/inflammation-related cytokines. Using an in vitro model we observed similar alterations in cytokine expression, indicating that this may be a cell autonomous function of Dsg1.

1. Harmon, R.M., C.L. Simpson, J.L. Johnson, J.L. Koetsier, A. Dubash, N. Najor, O. Sarig, E. Sprecher, and **K.J. Green** (2013). Desmoglein-1/Erbin interaction suppresses Erk activation to support epidermal differentiation. *J. Clin. Invest.* 123: 1556-70. PMC3613912. (*Commentary by Hammers, C.M. and J.R. Stanley. Desmoglein-1, differentiation, and disease. Highlighted in F1000)*
2. Dubash, A.D., J.L. Koetsier, E.V. Amargo, N.A. Najor, R.H. Harmon, and **K.J. Green**. (2013). The GEF Bcr activates RhoA/MAL signaling in keratinocytes to promote keratinocyte differentiation via Desmoglein-1. *J. Cell Biol.* 202: 653-66. PMC3747303.
3. Samuelov, L., O. Sarig R.M. Harmon, D. Rapaport, A. Ishida-Yamamoto, O. Isakov, J.L. Koetsier, A.Gat, I. Goldberg, R. Bergman, R. Spiegel, O. Eytan, S. Geller, S. Peleg, N. Shomron, C.S.M. Goh, N. J. Wilson, F.J.D. Smith, E. Pohler, M.A. Simpson, W.H. I. McLean, A.D. Irvine, M. Horowitz, J.A. McGrath, **K.J. Green*** and E. Sprecher*. (2013). Desmoglein 1 membranal deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat. Genet*. 45: 1244-8. (*Co-corresponding authors). PMC in process. (*Recommended in F1000.)* PMC3791825
4. Arnette, C., J.L. Koetsier, P. Hoover, S. Getsios, and **K.J. Green**. (2016). In vitro Model of the Epidermis: Connecting Protein Function to 3D Structure. *Meth. Enzymol.* 569: 287-308. PMC4870045.

Intercellular Junction Assembly and Dynamics in Homeostasis and Disease: Our lab advanced the use of optical imaging methods to evaluate the dynamics of desmosomal proteins in living cells, and to establish how these dynamics are altered by human disease mutations and in tumor cells to mediate functional differences in adhesion strengthening. We determined that in keratinocytes, desmogleins and desmocollins traffic independently on microtubules via kinesin-1 and -2 respectively, towards sites of cell-cell contact. The plaque components that associate with the cytoplasmic tails of the cadherins, on the other hand, are assembled into non-membrane bound precursors that translocate in an actin-dependent manner to sites of junction assembly where they associate through plakophilins with the transmembrane complex. Using a combination of imaging and biochemistry, we advanced our knowledge about how inherited mutations in desmosome molecules cause human skin and heart disease, including Arrhythmogenic Cardiomyopathy (AC), which causes sudden death in young individuals. We identified the microtubule (MT) plus tip protein, end binding protein 1 (EB1), as a novel binding partner of the desmoplakin N-terminus, a "hot spot" for disease causing mutations. Mutations in this region interfere with EB1 binding, resulting in a loss of MT cortical capture and a failure to form gap junctions. We also identified arginine methylation as a novel posttranslational modification in the IF binding domain of desmoplakin. We showed that phosphoserines generated as a result of processive phosphorylation via GSK3beta cooperate with arginines to recruit kinases and methyltransferases critical for regulating desmoplakin's dynamic association with IF. An AC mutation in one of these sites interferes with DP's dynamic association with IF, delaying its assembly into remodeling desmosomes, and leading to features of AC in a transgenic mouse model. These data also implicate desmoplakin as a signaling scaffold that properly positions and regulates the activities of enzymes important for junction dynamics and, more broadly, cell behavior in remodeling tissues.

1. Godsel, L.M., S.N. Hsieh, E.V. Amargo, A.E. Bass, L.T. Pascoe-McGillicuddy, A.C. Huen, M.E. Thorne, C.A. Gaudry, J.K. Park, K. Myung, R.D. Goldman, L. Chew, and **K.J. Green**. (2005). Desmoplakin assembly dynamics in 4D: multiple phases differentially regulated by intermediate filaments and actin. *J. Cell Biol.* 171: 1045-1060.
2. Nekrasova, O.E., E.V. Amargo, Smith, W.O. Smith, J. Chen, G.E. Kreitzer, and **K.J. Green.** (2011). Desmosomal cadherins utilize distinct kinesins for assembly into desmosomes. *J. Cell Biol.* 195: 1185-203. PMC3246898. *(Highlighted in Biosights video: "A Twin-Track Approach to Building Desmosomes"*

http://jcb.rupress.org/content/195/7/1185/suppl/DC2; *featured in Journal Club* http://jcb.rupress.org/content/195/7/1185/suppl/DC3*).*

3. Patel, D, A. Dubash, and G. Kreitzer and **K.J. Green** (2014). Disease mutations in desmoplakin inhibit Cx43 membrane targeting mediated by desmoplakin-EB1 interactions. *J. Cell Biol.* 206: 779-97. *(Featured in JCB Biobytes).*
4. Albrecht, L.V., L. Zhang, J. Shabanowitz, E. Purevjav, J.A. Towbin, D.F. Hunt, and **K.J. Green**. (2015). Methylation-mediated modulation of desmoplakin-cytoskeletal interactions and cardiocutaneous disease. *J. Cell Biol.* 208: 597-612. (Cover photo; highlighted in "In this Issue". Desmoplakin's tail gets the message. *J. Cell Biol.* 2015. 208: 494.

Cell Adhesion Signaling and Cancer: While the role of classic cadherins in both promoting and suppressing tumor progression has been well-studied, less is known about how desmosomes participate in tumor growth or metastasis. Our work has shown that in head and neck cancer, desmosomal cadherins participate in bi-directional signaling with receptor tyrosine kinases. While Dsg1 suppresses MAPK signaling to promote differentiation, EGFR elevates desmosomal cadherin endocytosis and turnover in tumor cells to attenuate cadherin signaling functions, reduce adhesion strength and promote migration. The loss of Dsg1 in cancers of the head and neck has been associated with poor patient prognosis, possibly due to loss of its functions in promoting differentiation and suppressing cytokine production. UV exposure specifically reduces expression of Dsg1, but not E-cadherin or other desmosomal cadherins, associated with reduced binding of p63 to previously undescribed enhancer regions in the Dsg1 gene. The resulting shift away from differentiation may create an environment permissive for progression of SCCs and melanoma. The desmosomal armadillo proteins plakoglobin, PKP2 and PKP3 also participate in regulation of cell motility and adherens junction assembly status in tumor cells, through regulation of tyrosine kinase and small Rho GTPases.

1. Klessner, J.*, B. Desai*, E.V. Amargo, S. Getsios and **K.J. Green**. (2009) EGFR and ADAM17 Cooperate to Regulate Shedding and Endocytic Trafficking of the Desmosomal Cadherin Desmoglein 2. *Mol. Biol. Cell.* 20(1):328-37 **Authors contributed equally to this work.*
2. Todorović, V., B. V. Desai, M.J. Schroeder Patterson, E.V. Amargo, A. D. Dubash, T. Yin, J.C.R. Jones and **K. J. Green**. (2010). Plakoglobin regulates cell motility through distinct matrix-dependent Src and Rho signaling pathways. *J. Cell Sci.* 123:3576-86. PMC2951470.
3. Johnson J, Koetsier J, Sirico A, Agidi A, Antonini D, Missero C, **Green KJ..** (2014) The desmosomal protein desmoglein 1 aids recovery of epidermal differentiation after acute ultraviolet light exposure. *J. Invest. Derm.* 134: 2154-62. PMC4102640.
4. Sassano, A., E. Mavrommatis, A.D. Arslan, B. Korczynska, E.M. Beauchampm, S. Khuon, T.L. Chew, **K.J. Green**, H.G. Munshi, A.K. Verma and L.C. Platanias (2015). Human schlafen 5 (SLFN5) is a regulator of motility and invasiveness of renal cell carcinoma cells. *Mol. Cell. Biol.* 35: 2684-98. PMC4524119.

Link to My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kathleen.green.1/bibliography/40768970/public/?sort=date&direction=ascending

D. Research Support

NIH R37 (MERIT) AR043380 (Green, PI) 4/1/11 - 3/31/21
Desmoplakin Assembly and Function in Epidermis
The goals of this proposal are to determine how desmoplakin and its associated armadillo proteins in the plakophilin (PKP) family act as scaffolds to localize and harness the activities of signaling mediators required for junction assembly and epidermal differentiation, and how DP/PKP deficiency and mutations affecting DPPKP interactions contribute to disease pathogenesis by interfering with their structural and signaling functions.

NIH R01 AR041836 (Green, PI) 9/1/12 - 8/31/17
Function of Desmoglein 1/Pemphigus Foliaceus Antigen
The major goals of this project are to determine the mechanism of Dsg1 transport to the plasma membrane, determine how Dsg1 dampens MAPK signaling to promote epidermal differentiation, and test the importance of

this pathway in striate palmar plantar keratoderma (SPPK), and determine how Dsg1 and its associated protein Erbin regulate cytoskeletal remodeling pathways to promote epidermal differentiation and morphogenesis.

NIH R01 CA122151 (Green, PI) 9/11/12 - 7/31/17
Regulation of Desmosomal Cadherins in Oral Cancer
The major goals of this proposal are to test the hypothesis that loss of desmoglein 1 during oral cancer progression results in elevated EGFR/Erk signaling and a consequent shift in the balance between differentiation and proliferation pathways, and to determine how bi-directional interactions between Dsgs and ADAM family members further regulate tumor progression.

NIH R56 AR044016 (Troyanovsky, PI) 9/1/15 - 8/31/16
Inter-junctional signaling in epithelial junctional complex
Dr. Green is co-I of this project, which is to determine the mechanism by which remodeling of the actin cytoskeleton and its associated proteins directs the ordered assembly of nectin junctions, tight junctions and desmosomes.
Role: Co-I

NIH T32 CA009560 (Green, PI) 7/1/12 - 6/30/17
Carcinogenesis Training Program
The major goal of this project is to provide training for predoctoral students in investigations of the mechanisms of tumorigenesis and carcinogenesis.

NIH P30 CA60553 (Platanias, PI) 8/1/13 - 7/31/18
The Robert H. Lurie Comprehensive Cancer Center
The goals of this Cancer Center Support Grant are to conduct and support cancer research and to integrate cancer-related research throughout the university; to coordinate and integrate cancer-related activities of the University including community outreach initiatives; to develop and conduct cancer education programs; to promote and participate in state-of-the-are care of cancer patients at the affiliated hospitals of the McGaw Medical Center of Northwestern University and; to develop and implement the initiatives in cancer prevention and control research.
Role: Associate Director for Basic Sciences

NIH P30 AR057216 (Paller, PI) 8/1/14 - 6/30/19
Northwestern Univ. Skin Disease Research Core Center
Role: Dr. Green is the Tissue Engineering Core Co-Director (Core B), the major goal of which is to provide cells and instruction related to investigations in cutaneous biology research at Northwestern.

Completed Research Support

Leducq Foundation (Jalife, Hatem, PIs) 10/1/09-9/30/15
Structural Alterations in the Myocardium and the Substrate for Cardiac Fibrillation
This Transatlantic Research Network proposes research towards improving mechanistic insight into arrhythmogenesis and ultimately developing and clinically testing novel approaches for the prevention and treatment of cardiac arrhythmias. (Dr. Green is a Core Member).

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