Kenneth L Rock

Address: University of Massachusetts Medical School Worcester

Country: USA

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
Washington University	B.A.	1974	Biology
University of Rochester, NY	M.D.	1978	Medicine
Peter Bent Brigham Hospital		1979-1983	Pathology

A. Personal Statement

One major focus of the principle investigator's laboratory is on antigen presentation. Antigen presentation is the process whereby peptides are produced and displayed on MHC molecules to T lymphocytes. It controls whether or not T cell responses are generated and if they are, their specificity and magnitude. In addition, it controls the selection of T cells during development. By controlling these events antigen presentation plays an essential role in viral host defense and indeed polymorphisms in the genes in this pathway have been linked to infectious and autoimmune diseases. Dr. Rock's laboratory has established many of the key underlying mechanisms in these processes including the role of the proteasomes/immunoproteasomes, cytosolic aminopeptidases, and ERAP1 in MHC class I presentation, the cellular and cell biological basis of cross presentation, and the underlying mechanisms of antigen presentation in T-B cell interactions. The other area of focus is to elucidate how cell death and danger signals influence immune responses and more broadly how sterile stimuli stimulate innate immunity. These processes are thought to underlie the development of innate and adaptive immune responses to injured cells. It also underlies the sterile inflammation that is thought to underlie the pathogenesis of a number of diseases. In this area, he established the molecular identity of the first endogenous danger signal (MSU) and a key common pathway, involving IL-1 and inflammasomes, through which many structurally distinct stimuli cause sterile inflammation. Dr. Rock is an ISI highly cited

researcher. His work has been recognized with high citation indexes (e.g. an overall H-index of 69 and a top primary paper cited >2,500 times - citation #2.b., below); paper selected and reprinted as a seminal work in the "Pillers of Immunology" series of J. of Immunology (citation 1.b., below); several commentaries in leading journals (e.g. News & Views Nature), invited reviews (e.g. Nature) and presentations at national and international meetings.

B. Positions and Employment

1982-1983	Instructor in Pathology, Harvard Medical School, Boston, MA
1983-1986	Assistant Professor of Pathology, Harvard Medical School, Boston, MA
1986-1996	Associate Professor of Pathology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
1996-	Professor and Chairman of Pathology, UMass Medical School, Worcester, MA

Other Experience and Professional Memberships

1984-Present	American Association of Immunologists
1989-1997	Co-chairman, Animal Care and Use Committee; Dana Farber Cancer Institute
1990-1997	American Association for Laboratory Animal Science.
1990-Present	American Association for the Advancement of Science
1992-1999	Scientific founder, Proscript Inc. (MyoGenics Inc.), Cambridge, MA. (acquired by Millennium Pharmaceuticals)
1993-1996	Membership Committee, American Association of Immunologists
1994-2005	Scientific founder, Corixa Corp., Seattle, WA (acquired by GSK)
1995-1997	Block Co-Chairman, then Block Chairman, Program Committee, American Association of Immunologists.
1997-Present	College of American Pathologists
1997-Present	United States and Canadian Academy of Pathology
1997-Present	New England Society of Pathologists
2000-2005	Founding scientific board, Diamed (formerly SPRL), Cambridge, MA
2001	Nominating Committee, American Association of Immunologists
2003-2007	Cancer Immunology Task Force, American Association of Cancer Research

2006 Nominating Committee, American Association of Immunologists

2007-2010 Finance Committee, American Association of Immunologists

2010-2016 Board of Scientific Counselors, National Cancer Institute

Honors

1974 Summa cum laude, B.S., Washington University, St. Louis, MO

1974 Phi Beta Kappa

1998 Merit Award, NIH

2003 Outstanding educator award, UMass Medical School

2003 Benacerraf Lecture, Harvard Medical School

2009 Ernest Witebsky Lecture and Award

C. Contribution to Science

1. T-B cell collaboration and B cell antigen presentation. At the time of our studies, it was known that a B cell epitope needed to be physically linked to a T cell protein antigen in order to generate T dependent antibody responses ("happen-carrier effect), and it was incorrectly thought that this molecular configuration was needed to bridge B and T cells. My lab, in collaboration with Abbas, carried out the first studies to demonstrate that the underlying mechanism for the hapten-carrier effect was surface immunoglobulin binding of the hapten, which then efficiently delivered the linked T cell antigen into the MHC II antigen processing pathway. This work was recognized as a "Pillars of Immunology" contribution and has been cited >400 times.

a. **Rock KL**, Benacerraf B, and Abbas AK. Antigen-presentation by hapten-specific B lymphocytes. I. Role of surface immunoglobulin receptors. 1984. J. Exp. Med. 160:1102-1113. (as of May 2018, cited 466 times)

b. **Rock, KL**, Benacerraf, B. and Abbas, AK. 2007 Pillars of Immunology article: Antigen presentation by hapten-specific B lymphocytes: 1. Role of surface immunoglobulin receptor. J. Immunol. 197: 7194-205 (reprinted)

c. Abbas AK, Haber SI, and **Rock KL**. Antigen-presentation by hapten-specific B lymphocytes. II. Specificity and properties of antigen-presenting B lymphocytes, and function of immunoglobulin receptors. 1985. J. Immunol. 135:1661-1667. (as of May 2018, cited 107 times)

2. The role of the ubiquitin-proteasome pathway in antigen presentation. At the time we initiated our studies it was unknown how peptides were generated for MHC I presentation and my lab was the first to elucidate this mechanism. We showed that ubiquitination of an antigen was needed for antigen presentation, implicating the ubiquitin-proteasome pathway (cited >550 times). We then showed that the proteasome was required to generate the majority of MHC I-presented peptides (cited >2,400 times). In related work, John Monaco had discovered 3 new INF□-inducible subunits of the proteasome that assembled into what became called the Immunoproteasome. The function and significance of these subunits was unknown. Contemporaneously, our group (a close collaboration between my lab and Fred Goldberg's) and Monaco's lab elucidated that the immunoproteasome subunits encoded the active sites of the proteasome and functioned in ways that generally enhanced the generation of MHC I-presented peptides (cited >575 times). Also of note, our studies above described the first proteasome inhibitors; these agents were subsequently developed by biotech into the drug Velcade, which has provided a major advance in the treatment of multiple myeloma.

a. Michalek, M.T., Grant, E., Gramm, C., Goldberg, and **Rock, K.L**. A role for the ubiquitin-dependent proteolytic pathway in MHC class I-restricted antigen presentation. 1993. Nature. 363: 552-554 (as of May 2018, cited 365 times)

b. **Rock, K.L**., Gramm, C., Rothstein, L., Clark, K., Stein, R., Dick, L., Hwang, D., and Goldberg, A.L. Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC-class I molecules. 1994. Cell 78: 761-771 [as of May 2018, cited >2,531)

c. Gaczynska, M., **Rock, K. L.,** and Goldberg, A. L. □-Interferon and Expression of MHC genes regulate the peptidase activities of proteasomes. 1993. Nature. 365: 264-267 (as of May 2018, cited 641)

d. Kincaid, E.Z., Che, J.W., York, I., Escobar, H., Reyes-Vargas, E., Delgado, J.C., Welsh, R.M., Karow, M.L., Murphy, A.J., Valenzuela, D.M., Yancopouloos, G.D. and **Rock, K.L**. 2012 Mice completely lacking immunoproteasomes display major alterations in antigen presentation. Nature Immunology. 13:129-35 (as of May 2018, cited 161 times)

3. Discovery of ERAP1 and the trimming of antigenic peptides. At the time we discovered the role of the proteasome in antigen processing, it was unknown whether this particle was the sole protease involved in generating presented peptides or whether additional peptidases participated in this process. My lab was the first to show that proteasomes were responsible for generating the proper C-terminal cleavage of an epitope in vivo, but that other peptidases were involved in trimming the N-terminus of presented peptides (cited 251 times). This led us to initiate studies to identify the 2nd enzyme(s) needed for MHC I antigen processing. Contemporaneously, we and our collaborators and Shastri's lab discovered that the major N-terminal trimming peptidase was ERAP1 (ERAAP) (cited >400 times). We and others showed ERAP1 is important for responses in mice and influences their specificity (cited 125 times). Consistent with these findings, subsequent studies by others have found that ERAP1 polymorphisms are important genetic risk factors for some autoimmune diseases and cancer.

a. Craiu, A. Akopian, T., Goldberg, A., and **Rock, K.L**. Two distinct proteolytic processes in the generation of an MHC class I-presented peptide. 1997. Proc. Natl. Acad. Sci. USA. 94:10850-10855 (as of May 2018, cited 286 times)

b. Saric, T., Chang, S-C, Hattori, A., York, I.A., Markant,S., **Rock, K.L**., Tsujumoto, M., and Goldberg, A.L. ERAP1, An interferon g-induced aminopeptidase in the endoplasmic reticulum, that trims precursors to MHC class I-presented peptides. 2002 Nature Immunology, 3: 1169-1176 (as of May 2018, cited 525 times)

c. York, I.A., Chang, S-C., Saric, T., Keys, J.A., Favreau, J.M., Goldberg, A.L. and **Rock, K.L.** The interferon-inducible ER aminopeptidase ERAP1 enhances or limits antigen presentation by trimming peptides to 8-9 residues. 2002 Nature Immunology, 3: 1177-1184 (as of May 2018, cited 481 times)

d. York, IA, Brehm, MA, Zendzian, S., Towne, CF., and **Rock, KL**. 2006 ER-Aminopeptidase I (ERAP1) trims MHC class I-presented peptides in vivo and plays an important role in establishing immunodominance. Proc. Natl. Acad. Sci. USA. 103: 9202-7 (as of May 2018, cited 156 times)

4. Discovery of the cellular basis and molecular mechanisms of cross presentation. At the time of our studies, it was thought MHC I molecules only presented peptides derived from a cell's endogenous proteins but not exogenous ones (unless they were already peptides). However, in 1976 Bevan had reported an obscure phenomenon, called cross priming, in which CD8 T cell responses could be generated to minor transplant antigens that were restricted to the host MHC I molecules. This led us to hypothesize that some specialized antigen presenting cells might be able to process exogenous antigens for presentation on MHC I molecules. Testing this hypothesis led my lab to discover that there were indeed antigen presenting cells that could cross present antigens (cited 370 times) and to identify these cells as dendritic cells and macrophages. We then went on to elucidate the underlying molecular pathways (the phagosome-to-cytosol transfer of antigens - cited 895 times) and Cat S vacuolar pathway (cited 307 times). Many initially thought that this cross presentation pathway was of little physiological importance. However, we then showed that it was required to generate CD8 immunity to tissue tropic viral infections (cited 575 times) and others showed this for tumor and transplant immunity. This pathway is also of potential importance for the development of vaccines that elicit CD8 T cell responses.

a. **Rock KL**, Gamble S, and Rothstein L. Presentation of exogenous antigen with class I major histocompatibility molecules. 1990. Science 249:918-921. (as of May 2018, cited 388 times)

b. Kovacsovics-Bankowski, M., and **Rock, K.L.** A phagosome-to-cytosol pathway for exogenous antigens presented on MHC class I molecules. 1995. Science. 267: 243-246. (as of May 2018, cited 917 times)

c. Sigal, LJ, Crotty, S., Andino, R., and **Rock, K.L.** Cytotoxic T cell immunity to virus-infected non-haematopoietic cells requires presentation of exogenous antigen. 1999. Nature 398: 77-80 (as of May 2018, cited 642 times)

d. Shen, L., Sigal, LJ. Boes, M., and **Rock, KL**. Critical role of cathepsin S in TAP-independent MHC class I cross presentation in vivo. 2004 Immunity. 45: 218-25 (as of May 2018, cited 336)

5. Danger signals and sterile inflammation. At the time we initiated our studies, Matzinger had theorized that the immune system recognized and responded to cell injury and death, however there was no experimental support for this concept. Studies from our lab discovered that injured cells released DAMPs (AKA danger signals or endogenous adjuvants) that stimulated both adaptive and innate immune responses. We purified the first DAMP and determined its molecular identity as uric acid. We then elucidated that dying cells and particles induced sterile inflammation and by stimulating the production of IL-1 (Tschopp also discovered this for uric acid crystals). This work has stimulated many studies on IL-1 production (inflammasomes, etc) and effects in sterile inflammation, to which we have continued to contribute, and to the use of IL-1 blockers in the uric acid-based disease of gout.

a. Shi Y., Zheng, W., and **Rock KL**. Cell injury releases endogenous adjuvants that stimulate cytotoxic T cell responses. 2000 Proc. Natl. Acad. Sci. USA 97: 14590-95 (as of May 2018, cited 260 times)

b. Shi, Y., Evans, JE. and **Rock, KL**. Molecular identification of a danger signal that alerts the immune system to dying cells. 2003 Nature, 425: 516-21 (as of May 2018, cited >1,606 times)

c. Chen, C-J., Shi, Y., Hearn, A., Fitzgerald, K., Golenbock, D., Akira, S., and **Rock, K.L**. 2006 MyD88-dependent interleukin 1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. J. Clin Invest. 116:2262-71. (as of May 2018, cited 431 times)

d. Chen, C-J., Kono, H., Golenbock, D., Reed, G., Akira, S., and **Rock, K.L**. 2007. Identification of a key pathway required for the sterile inflammatory response triggered by necrotic dying cells. Nature Medicine. 13:851-6 (as of May 2018, cited 759 times)

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/kenneth.rock.1/bibliography/40520321/public/?sort=date&direction=ascending