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Date and Place of Birth:

April 25, 1942; Mumbai, India

Citizen:

USA

Education

1961	B.Sc. University of Mumbai, Mumbai, India. Chemistry
1963	M.S. California Institute of Technology, Pasadena, CA. Chemistry
1968	PhD. New York University, New York, NY. Chemistry

Postdoctoral Training:

1967	New York Univ. Medical School New York, NY. Biochemistry.
1968 - 1969	AT&T Bell Laboratories, Murray Hill, NJ. Biophysics.

Appointments:

1970 - 1984	Member of Technical Staff, Polymer Chemistry Department, AT&T Bell Laboratories, Murray Hill, NJ
1984 - 1992	Professor of Biochemistry & Molecular Biophysics, College of Physicians & Surgeons, Columbia University, New York, NY
1992 -	Member, Structural Biology Program Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York
1994 -	Professor, Graduate Program in Biochemistry & Structural Biology, Weill School of Medical Sciences, Cornell University, New York, NY

Honors:

1961 - 1963	Jamshetjee N. Tata Fellow
1983	AT&T Bell Laboratories Distinguished Technical Staff Award
1992 -	Abby Rockefeller Mauzé Chair in Experimental Therapeutics (MSKCC)
1997	Distinguished Alumnus Award, New York University
1997 - 1999	Harvey Society (Vice-President 97-98; President 98-99)
2013	NIH Directors Transformative R01 Award (with Thomas Tuschl and Uwe Ohler)
2014	2014 FEZANA Jamshed and Shirin Guzdar Excellence in Profession Award

Academy Memberships

2009	Member, National Academy of Sciences, USA
2014	Member, American Academy of Arts and Sciences, USA

Named/Plenary/Keynote Lectureships (since 2010)

2010	John D. Roberts Lecture, California Institute of Technology, Pasadena, CA

2011 Keystone Symposium on RNA Silencing, Monterey, CA
2011 C. C. Tan Lecture, Fudan University, Shanghai, China
2012 IAS Distinguished Lecture, Hong Kong Univ. of Science & Tech., Hong Kong, China
2013 Epigenetics Symposium, University of Michigan, Ann Arbor, MI
2013 NCI Eminent Lecture, Center for Cancer Research, National Cancer Institute, USA
2014 Kiran Mazumdar Shaw Lecture, Inst. Bioinform. & Applied Biotech., Bangalore, India
2014 Dean's Lecture, Virginia Commonwealth University, Richmond, VA
2014 Master Forum Lecture, Chinese Academy of Medical Sciences, Beijing, China
2014 Cell Press Lab Links Epigenetics Symposium, Beijing, China
2014 IUBMB International Conference, Academica Sinica, Taipei, Taiwan
2014 Shanghai Structural Biology Network Meeting, Shanghai, China
2015 Einstein Professorship of Chinese Academy of Sciences, China
2015 Shizhang Bei Lectureship, CAS Institute Biophysics, Beijing, China
2015 Science Across China Lectureship, Yunnan University, Kunming, China
2015 Joint Life Sciences Center, Tsinghua - Peking Universities, Beijing, China

External Review Committees:

1984 - National Institutes of Health, Bethesda, MD
• Member, Molecular and Cellular Biophysics Study Section (84-88)
• National Cancer Institute, Board of Scientific Counselors-B (00-05)
1989 - 1996 Howard Hughes Medical Institute, Chevy Chase, MD
• Member, Scientific Review Board - Structural Biology (89-92)
• Member, Medical Advisory Board (93-96)
2009 - Scientific Advisory Board, European Institute of Chemistry & Biology, Bordeaux, France
2010 - 2011 Scientific Advisory Board, Epinova, GlaxoSmithKline, Stevenage, United Kingdom
2011 - Scientific Advisory Board, Institute for Research in Biomedicine, Barcelona, Spain
2015 Scientific Advisory Board, Joint Center for Life Sciences, Tsinghua-Beijing Universities, Beijing, China

Personal Statement

I received my PhD in Chemistry from New York University (NYU) in 1968 for research in the photochemistry. I decided next to shift the emphasis of my research to the life sciences and hence completed postdoctoral training (one year) in Biochemistry at NYU School of Medicine followed by postdoctoral training (two years) in Biophysics at AT&T Bell Laboratories. I was next promoted to permanent Member of Technical Staff at Bell Labs and spent the next 15 years undertaking NMR-based studies of the structure and dynamics of cyclic peptides, proteins and nucleic acids. I moved to Columbia University Medical School in 2004 as a tenured Professor of Biochemistry and Molecular Biophysics where my group spent the next 8 years doing NMR-based research on DNA mismatches, bulges and junctions, on DNA triplexes and G-quadruplexes, and drug-DNA complexes. I was recruited in 1992 as a tenured Member to the Cellular Biochemistry and Biophysics Program at the Memorial Sloan-Kettering Cancer Center to set up a Structural Biology component to the program. My group's research during the 1990s focused on NMR-based studies of covalent chiral carcinogen-DNA adducts, and complexes of antibiotics and peptides with natural and *in vitro* selected RNA targets.

My laboratory began to increasingly use x-ray crystallography starting around 2000 with the emphasis initially on RNA-mediated gene regulation. My group determined the higher order architectures of compact riboswitch sensing domains bound to amino acids, metabolites and ions, as well as elucidated how RNA containing only four nucleotides could generate pockets capable of recognizing specific ligands and discriminating against closely-related analogs. In the RNA silencing area, my group made fundamental discoveries over the next decade related to the structural biology of Argonaute proteins and their complexes with guide DNA and target RNAs, thereby providing mechanistic insights into the nucleation, propagation and cleavage steps of Ago-mediated cleavage of mRNA [collaboration with Thomas Tuschl (Rockefeller) and David Bartel (MIT)]. More recently, my group extended its research to Dicer proteins where we identified a phosphate-binding pocket in human Dicer [collaboration with Narry Kim (Seoul National University)] an inside-out non-canonical pathway of dsRNA cleavage by

budding yeast Dicer, in contrast with to an outside-in pathway for Dicer's cleavage activity in higher eukaryotes [collaboration with David Bartel (MIT)]. My group's efforts also focused on structure determination of disease-related protein-RNA complexes, thereby defining the principles underlying the specificity of intermolecular recognition and the role of protein dimerization in facilitating complex formation [collaboration with Thomas Tuschl (Rockefeller)].

In 2005 my group initiated a comprehensive research program in epigenetic regulation focused on understanding the diversity of mechanisms for site- and state-specific readout of histone marks by writer, reader and eraser protein modules. Initial efforts with single effector modules were expanded over time to multivalent readout at the histone peptide and nucleosomal level [collaboration with David Allis (Rockefeller)]. These studies were extended to the identification of small molecules that targeted effector pockets with high affinity and specificity, and elucidation of the role of histone chaperones and chromatin remodelers in epigenetic regulation. My group initiated our research on DNA methylation mark-mediated epigenetic regulation in 2010 by focusing our structural studies on a pair of DNMT1-DNA complexes, whereby we established how a combination of autoinhibitory and productive mechanisms ensured the high fidelity of DNMT1-mediated maintenance DNA methylation. This research was next extended to studies that provided mechanistic insights into plant proteins that mediate the role of polymerases pol-IV and pol-V in RNA-directed DNA methylation in *A. thaliana* [collaboration with Steve Jacobsen (UCLA)]. More recently, structure-function studies have provided the molecular basis underlying the process whereby CHG DNA methylation in *A. thaliana* is controlled by the H3K9 methylation mark through a self-reinforcing loop between DNA methyltransferase CMT3 and H3K9 histone methyltransferase Kryptonite [collaboration with Steve Jacobsen (UCLA)].

My group initiated a structural biology program in 2003 on lipid transfer proteins that acquire and release neutral glycosphingolpids and charged phosphosphingolipids during lipid intermembrane transfer and presentation processes. Our studies established the molecular basis underlying differentiation of neutral from charged lipids by their respective head group recognition centers, and defined the alignment of one or both lipid chains within a molded-to-fit hydrophobic tunnel, thereby supporting a cleft-like gating mechanism, whereby lipid chains sequentially entered and departed the tunnel in the membrane-associated state [collaboration with Rhoderick Brown (Hormel Institute)].

More recently, my group has turned its attention to the field of pattern recognition receptors that sense double-stranded nucleic acids in the cytosol, thereby triggering a cascade of events that activate the innate immune response. Our efforts have focused on cGAS, the metazoan sensor of cytosolic dsDNA, the second messenger cGAMP and the adaptor STING [collaboration with Thomas Tuschl (Rockefeller) and Winfried Barchet (University Hospital-Bonn)]. Our structural studies identified cGAMP, produced by DNA-activated cGAS from GTP and ATP, to be c[G(2',5')pA(3',5')p], that contained an unanticipated 2',5' linkage at the GpA step. Our research was next extended to STING activation by cGAMP and targeting by the anti-viral agent DMXAA.

Contributions to Science:

(Papers and reviews: 500+; Google Scholar h index: 100+)

We list below primarily relevant papers published in the 2003 to 2015 time frame.

Riboswitches and Ribozymes

The role of RNA in information transfer and catalysis highlights its dual functionalities. Our group has determined the higher order architectures of compact riboswitch sensing domains bound to amino acids, metabolites and ions, thereby defining the principles associated with intermolecular recognition, as well as elucidated how RNA containing only four nucleotides could generate pockets capable of recognizing specific ligands and discriminating against closely-related analogs [collaborator: Hashim Al-Hashimi (Duke).

Serganov, A., et al. & Patel, D. J. (2004). Structural basis for discriminative regulation of gene expression by adenine- and guanine-sensing mRNAs. ***Chem. Biol.*** 11, 1729-1741.

Serganov, A., et al. & Patel, D. J. (2006). Structural basis for gene regulation by a thiamine pyrophosphate-binding riboswitch. ***Nature*** 441, 1167-1171.

Serganov, A. & Patel, D. J. (2007). Ribozymes, riboswitches and beyond: regulation of gene expression without proteins. ***Nat. Rev. Genetics*** 8, 776-790.

Serganov, A., Huang, L. & Patel, D. J. (2008). Structural insights into amino acid binding and gene control by a lysine riboswitch. ***Nature*** 455, 1263-1267.

Serganov, A., Huang, L. & Patel, D. J. (2009). Coenzyme recognition and gene regulation by a FMN riboswitch. ***Nature*** 458, 233-237.

Huang, L., Serganov, A. & Patel, D. J. (2010). Structural insights into ligand recognition by a sensing domain of the cooperative glycine riboswitch. ***Mol. Cell*** 40, 774-786.

Pikovskaya, O., Polonskkaya, A., Patel, D. J. & Serganov, A. (2011). Structural principles of nucleoside selectivity in a 2'-deoxyguanosine. ***Nat. Chem. Biol.*** 7, 748-755.

Serganov, A. & Patel, D. J. (2012). Metabolite recognition principles and molecular mechanisms underlying riboswitch function. ***Ann. Rev. Biophys*.** 41, 343-370.

Ren, A., Rajashankar, K. & Patel, D. J. (2012). Fluoride ion encapsulation by Mg^{2+} and phosphates in a fluoride riboswitch. ***Nature*** 486, 85-89.

Ren, A. et al. & Patel, D. J. (2015). Structural and dynamic basis for low-affinity, high-selectivity binding of L-glutamine by the glutamine riboswitch. ***Cell Reports*** 13, 1800-1813.

Small self-cleaving ribozymes contain catalytic domains that accelerate site-specific cleavage/ligation of phosphodiester backbones. Our research on ribozymes has elucidated the role of geometric constraints, nucleophilic activation, stabilization of the transition state and protonation of the leaving group, together with in-line alignment and divalent cation coordination, to cleavage chemistry [collaborator: Ronald Micura (University of Innsbruck)].

Serganov, A. et al., Jaschke, A. & Patel, D. J. (2005). Structural basis for Diels-Alder ribozyme catalyzed carbon-carbon bond formation. ***Nature Struct. & Mol. Biol.*** 12, 218-224.

Ren, A., et al., Micura, R. & Patel, D. J. (2014). In-line alignment and Mg^{2+} coordination at the cleavage site of the twister ribozyme. ***Nat. Commun.***15: 5534.

Kosutic, M., et al., Patel, D. J., Kreitz, C. & Micure, R. (2015). A mini-twister variant and impact of residues/cations on the phosphodiester cleavage chemistry of this ribozyme class. ***Angew. Chemie Int. Edn*.** 54, 15128-15133.

RNA Silencing

Short RNAs, as regulators of cellular function, impact on the maintenance of genomic integrity and stability, on cell growth, differentiation and developmental processes, and on the antiviral RNA-silencing response. RNA silencing refers to small interfering RNA (siRNA)-mediated post-transcriptional gene regulation, resulting in the silencing of viral genes and transgenes. In the RNA silencing area, our group has made fundamental discoveries related to the structural biology of prokaryotic and eukaryotic Argonaute proteins and their complexes with guide and target strands, thereby providing mechanistic insights into the nucleation, propagation and cleavage steps of Ago-mediated cleavage of mRNA [collaborators: Thomas Tuschl (Rockefeller), David Bartel (MIT) and John van der Oost (Wageningen University, The Netherlands)].

Ye, K., Malinina, L. & Patel, D. J. (2003). Recognition of siRNA by a viral suppressor of RNA silencing. ***Nature*** 426, 874-878.

Ma, J-B., Ye, K. & Patel, D. J. (2004). Structural basis for overhang-specific small interfering RNA recognition by the PAZ domain. ***Nature*** 429, 318-322.

Ma, J. B., et al., Tuschl, T. & Patel, D. J. (2005). Structural basis for 5'-end-specific recognition of the guide RNA strand by the *A. fugidus* PIWI protein. ***Nature*** 434, 666-670.

Yuan, Y. R., et al., Tuschl, T. & Patel, D. J. (2005). Crystal structure of *Aquifex aeolicus* Argonaute provides unique perspectives into the mechanism of guide strand-mediated mRNA cleavage. ***Mol. Cell*** 19, 405-419.

Zhang, X., et al., Patel, D. J. & Chua, N-H. (2006). Cucumber mosaic virus-encoded 2b suppressor inhibits *Arabidopsis* AGO1 cleavage activity to counter plant defense. ***Genes Dev.*** 20, 3255-3268.

Wang, Y., et al., Tuschl, T. & Patel, D. J. (2008). Structure of the guide-strand-containing argonaute silencing complex. ***Nature*** 456, 209-213.

Wang, Y., et al., Tuschl, T. & Patel, D. J. (2008). Structure of an argonaute silencing complex with a seed-containing guide DNA and target RNA duplex. ***Nature*** 456, 921-926.

Wang, Y., et al., Tuschl, T. & Patel, D. J. (2009). Nucleation, propagation and cleavage of target RNAs in Ago silencing complexes. ***Nature*** 461, 754-761.

Nakanishi, K., Weinberg, D. E., Bartel, D. P. & Patel, D. J. (2012). Structure of yeast Argonaute with guide RNA. ***Nature*** 486, 368-374.

Shen, J., et al., Patel, D. J. & Hung, M. C. (2013). EGFR modulates miRNA maturation in response to hypoxia through phosphorylation of Ago2. ***Nature*** 497, 383-387.

Sheng, G., et al., van der Oost, J., Patel, D. J. and Wang, Y. (2014). Structure-based cleavage mechanism of *T. thermophiles* Argonaute DNA guide strand-mediated DNA target cleavage. ***Proc. Natl. Acad. Scis. USA.*** 111, 652-657.

Swarts, D. C., et al., Patel, D. J., Berenguer, J., Brouns, S. J. and van der Oost, J. (2014). DNA-guided DNA interference by prokaryotic Argonaute. ***Nature*** 507, 258-261.

Swarts, D. C., et al., Koonin, E. V., Patel, D. J. and van der Oost, J. (2014). The evolutionary journey of Argonaute proteins. ***Nat. Struct. Mol. Biol.*** 21, 743-753.

More recently, our group has extended our RNA silencing research to Dicer proteins where we identified a phosphate-binding pocket in human Dicer and its role in dsRNA cleavage chemistry [collaborator: Narry Kim (Seoul National University)], as well as identified an unanticipated inside-out non-canonical pathway of dsRNA cleavage by budding yeast Dicer, in contrast to an outside-in pathway for Dicer's cleavage activity in higher eukaryotes [collaborator: David Bartel (MIT)].

Weinberg, D., Nakanishi, K., Patel, D. J. & Bartel, D. P. (2011). The inside-out mechanism of Dicers from budding yeasts. ***Cell*** 146, 262-276.

Park, J. E., et al., Patel, D. J. & Kim, V. N. (2011). Dicer recognizes the 5'-end of RNA for efficient and accurate cleavage. ***Nature*** 475, 201-205.

Tian, Y., et al., Kim, V. N. & Patel, D. J. (2014). A phosphate-binding pocket within the platform-PAZ cassette of human Dicer. ***Mol. Cell*** 53, 606-616.

Our group has provided assistance to projects championed in the V. Narry Kim lab (Seoul National University, Seoul) on RNA 3'-end tailing including uridylation by TUTases and adenylation by WISPY.

Lee, M., t al., Patel, D. J. & Kim, V. N. (2015). Adenylation of maternally inherited microRNAs by Wispy. ***Mol. Cell*** 56, 696-707.

Lim, J., et al., Patel, D. J. & Kim, V. N. (2015). Uridylation by TUT4 and TUT7 marks mRNA for degradation. ***Cell*** 159, 1365-1376.

Kim, B., et al., Patel, D. J., Joo, C. & Kim, V. N. (2015). TUT7 controls the fate of precursor miRNAs by using three different uridylation mechanisms. ***EMBO J.*** 34, 1801-1815.

Our group has provided assistance to projects championed by the Alexei Aravin laboratory (Caltech) on piRNA biogenesis.

Le Thomas, A., et al., Patel, D. J. & Aravin, A.A. (2014). Trans-generationally inherited piRNAs trigger piRNA biogenesis by changing the chromatin of piRNA clusters and inducing precursor processing. ***Genes Dev.*** 28, 1667-1680.

Webster, A., et al., Patel, D. J. & Aravin, A. A. (2015). Aub and Ago3 are recruited to nuage through two mechanisms to form a ping-pong complex assembled by Krimper. ***Mol. Cell*** 59, 564-575.

Histone Mark-Mediated Epigenetic Regulation

Our group initiated a comprehensive research program in epigenetic regulation focused on understanding the diversity of mechanisms for site- and state-specific readout of histone marks by writer, reader and eraser protein modules [collaborators: David Allis (Rockefeller), Yang Shi (Harvard Medical School), and Or Gozani (Stanford)].

Li, H., et al., Allis, C. D. & Patel, D. J. (2006). Molecular basis for site-specific readout of H3 lysine 4 trimethylation by the BPTF PHD finger. ***Nature*** 442, 91-95.

Taverna, S. D., et al., Chait, B., Patel, D. J., Aitchison, J. D., Tackett, A. J. & Allis, C. D. (2006). Yng1 PHD finger binding to H3 trimethylated at K4 targets promotes NuA3 HAT activity at K14 of H3 and transcription at a subset of targeted ORFs. ***Mol. Cell*** 24, 785-796.

Li, H., et al., Allis, C. D. & Patel, D. J. (2007). Structural basis for lower lysine methylation state-specific readout by MBT repeats and an engineered PHD finger module. ***Mol. Cell*** 28, 677-691.

Taverna, S. D., et al., Allis, C. D. & Patel, D. J. (2007). How chromatin-binding modules interpret histone modifications: Lessons from professional pocket pickers. ***Nat. Struct. Mol. Biol*.** 14, 1025-1040.

Wang, G. G., et al., Patel, D. J. & Allis, C. D. (2009). Haematopoietic malignancies caused by dysregulation of a chromatin-binding PHD finger. ***Nature*** 459, 847-851.

Zhao, Q., et al., Patel, D. J., Allis, C. D., Cunningham, J. M. & Jane, S. M. (2009). PRMT5-mediated methylation of histone H4R3 recruits DNMT3A coupling histone and DNA methylation in gene silencing. ***Nat. Struct. Mol. Biol*.** 16, 304-311.

Iwase, S., et al., Patel, D. J., Li, H. & Shi, Y. (2011). ATRX links atypical histone methylation recognition mechanisms to human cognitive function. ***Nat. Struct. Mol. Biol.*** 18, 769-776.

Rajakumara, E., et al., Patel, D. J. & Shi, Y. (2011). PHD finger recognition of unmodified histone H3R2 links UHRF1 to regulation of euchromatic gene expression. ***Mol. Cell*** 43, 275-284.

Kuo, A. J., et al. Patel, D. J. & Gozani, O. (2012). ORC1 BAH domain links dimethylation of H4K20 to DNA replication licensing and Meier-Gorlin syndrome. ***Nature*** 484, 115-119.

Cai, L., et al. Patel, D. J., Allis, C. D., Strahl, B. D., Song, J. & Wang, G. (2013). An H3K36me3-containing Tudor motif of polycomb-like proteins mediates PRC2 complex targeting. ***Mol. Cell*** 49, 571-582.

Patel, D. J. and Wang, Z. (2013). A structural perspective of readout of epigenetic posttranslational modifications. ***Ann. Rev. Biochem*.** 82, 81-118.

Cheng, Z., et al., Gozani, O. & Patel, D. J. (2014). A molecular threading mechanism underlies jumonji lysine demethylase KDM2A regulation of methylated H3K36. ***Genes Dev***. **28**, 1758-1771.

Initial efforts on readout by single effector modules were expanded over time to multivalent readout at the histone peptide and nucleosomal levels [collaborators: David Allis (Rockefeller), Michelle Barton (M. D. Anderson Cancer Center) and Joan Massague (MSKCC)].

Ruthenburg, A. J., Li, H., Patel, D. J. & Allis, C. D. (2007). Multivalent engagement of chromatin modifications by linked binding modules. ***Nat. Rev. Mol. Cell Biol.*** 8, 983-994.

Wang, Z., et al., Allis, C. D. & Patel, D. J. (2010). Pro isomerization in MLL1 PHD3-Bromo cassette connects H3K4me3 readout to CyP33 and HDAC-mediated repression. ***Cell*** 141, 1183-1194.

Tsai, W-W., et al., Patel, D. J. & Barton, M. C. (2010). TRIM24 links recognition of a non-canonical histone signature to breast cancer. ***Nature*** 468, 927-932.

Ruthenburg, A., et al., Patel, D. J. & Allis, C. D. (2011). Recognition of a mononucleosomal histone modification pattern by BPTF via multivalent interactions. ***Cell*** 145, 692-706.

Xi, Q., et al., Patel, D. J. & Massague, J. (2011). A poised chromatin platform for Smad access to master regulators. ***Cell*** 147, 1511-1524.

These studies were extended to the identification of small molecules that targeted effector pockets with high affinity and specificity [collaborators: GlaxoSmithKline (UK) and Robert Roeder (Rockefeller)].

Kruidenier, L., et al., Patel, D. J., Lee, K., & Wilson, W. (2012). A selective H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. ***Nature*** 488, 404-408.

Sun, X-J., et al., Patel, D. J., Nimer, S. D. & Roeder, R. G. (2013). A stable transcription factor complex nucleated by dimeric AML1-ETO controls leukemogenesis. ***Nature*** 500, 93-97.

Wang, Z. and Patel, D. J. (2013). Small molecule epigenetic inhibitors targeted to histone lysine methyltransferases and demethylases. ***Quart. Rev. Biophys*.** 46, 349-373.

Various additional aspects of epigenetic regulation have been covered ranging from heterochromatin gene silencing to the DNA damage response [collaborators: David Allis (Rockefeller); Danesh Moazed (Harvard); Or Gozani (Stanford)].

Li, H., et al., Patel, D. J. & Moazed, D. (2009), An alpha motif of Tas3 C-terminus mediated RITS cis-spreading and promotes heterochromatin gene silencing. ***Mol Cell*** 34, 155-167.

Xiao, A., et al., Patel, D. J., Elledge, S. J. & Allis, C. D. (2009). WSTF regulates the DNA damage response of H2A.X via a novel tyrosine kinase activity. ***Nature*** 457, 57-62.

Noh, K. M., et al., Melnick, A, Patel, D. J., Li, H. and Allis, C. D. (2015). Engineering of a histone recognition domain in Dnmt3a alters the epigenetic landscape and phenotypic features of mouse ESCs. ***Mol. Cell*** 59, 89-103.

Chen, S., et al., Patel, D. J. and Gozani, O. (2015). The PZP domain of AF10 senses unmodified H3K27 to regulate DOT1L-methylation at H3K79. ***Mol. Cell*** 60, 319-327.

Recent efforts have focused on the elucidation of the role of histone chaperones in epigenetic regulation Current efforts are directed towards an understanding of the mechanism of chaperone-mediated histone shuttling, handover between different chaperone systems, and histone transfer onto and off DNA. [collaborators: David Allis (Rockefeller); Anja Groth (Copenhagen University, Denmark; Amine Nourani (University Laval, Quebec)].

Elsasser, S. J., et al., Allis, C. D. & Patel, D. J. (2012). DAXX histone chaperone envelops an H3.3/H4 dimer for H3.3-specific recognition. ***Nature*** 491, 560-565.

Chen, S., et al., Nourani, A. & Patel, D. J. (2015). Structure-function studies of histone H3/H4 tetramer maintenance during transcription by chaperone Spt2. ***Genes Dev*.** 29, 1326-1340.

Huang, H., et al., Groth, A. and Patel, D. J. (2015). A unique binding mode enables MCM2 to chaperone histones H3-H4 at replication forks. ***Nat. Struct. Mol. Biol.*** 22, 618-626.

DNA Mark-Mediated Epigenetic Regulation and RNA-Directed DNA Methylation

Methylation of cytosine in the CpG context has pronounced effects on gene expression with DNA methylation patterns established during embryonic development, faithfully maintained during subsequent somatic cell division. Our group initiated our research on DNA methylation mark-mediated epigenetic regulation by focusing our structural studies on DNMT1-DNA complexes, whereby we established how a combination of autoinhibitory and productive mechanisms ensured the high fidelity of DNMT1-mediated maintenance DNA methylation [collaborator: Steve Jacobsen (UCLA)].

Song, J., Rechkoblit, O., Bestor, T. H. & Patel, D. J. (2011). Structure of DNMT1-DNA complex reveals a role for autoinhibition in maintenance DNA methylation. ***Science*** 331,1036-1040.

Song, J., Teplova, M., Ishibe-Murakami, S. & Patel, D. J. (2012). Structural principles underlying DNMT1-mediated DNA methylation. ***Science*** 335. 709-712.

Zhong, X., et al., Patel, D. J. and Jacobsen, S. E. (2014). Molecular mechanism of action of plant DRM *de novo* DNA methyltransferases. ***Cell*** 157, 1050-1060.

This research was next extended to studies that provided mechanistic insights into plant proteins that mediate the role of polymerases RNA polymerases pol-IV and pol-V in RNA-directed DNA methylation [collaborator: Steve Jacobsen (UCLA)].

Law, J. A., et al., Patel, D. J. & Jacobsen, S. E. (2013). SHH1 recruits RNA polymerase-IV to RNA-directed DNA methylation targets. ***Nature*** 498, 385-389.

Johnson, L. M., et al., Patel, D. J. & Jacobsen, S. E. (2014). SRA/SET domain proteins link RNA polymerase V binding to DNA methylation. ***Nature*** 507, 124-128.

Various aspects of DNA-mediated epigenetic regulation have been investigated from readout of DNA methylation marks to non-CG methylation in plants [collaborator: Steve Jacobsen (UCLA)].

Rajakumara, E., et al., Reinberg, D., Patel, D. J. & Jacobsen, S. E. (2011). A dual flip out mechanism for 5mC recognition by the *Arabidopsis* SUVH5 SRA domain and its impact on DNA methylation and H3K9 dimethylation *in vivo.* ***Genes Dev.*** 25, 137-152.

Stroud, H., et al., Patel, D. J. & Jacobsen, S. E. (2014). The roles of non-CG methylation in Arabidopsis. ***Nat. Struct. Mol. Biol.*** 21, 64-72.

More recently, structure-function studies have provided insights into the molecular basis underlying the process whereby CHG DNA methylation in *A. thaliana* is controlled by the H3K9 methylation mark through a self-reinforcing loop between DNA methyltransferase CMT3 and H3K9 histone methyltransferase Kryptonite [collaboration with Steve Jacobsen (UCLA)].

Du, J., et al., Patel, D. J. & Jacobsen, S. E. (2012). Dual binding of chromomethylase BAH and chromo domains to H3K9me2-containing nucleosomes in the targeting of DNA methylation. ***Cell*** 151,167-180.

Du, J., et al., Patel, D. J. and Jacobsen, S. E. (2014). Mechanism of DNA methylation-directed histone methylation by KRYPTONITE. ***Mol. Cell*** 55, 495-504.

Du, J., Johnson, L. M., Jacobsen, S. E. and Patel, D. J. (2015). DNA methylation pathways and their crosstalk with histone methylation. ***Nat. Rev. Mol. Cell Biol.*** 16, 519-532.

Pattern Recognition Receptors Targeted to Cytosolic Nucleic Acids

Our group has recently turned its attention to the field of pattern recognition receptors that sense double-stranded nucleic acids in the cytosol, thereby triggering a cascade of events that activate the innate immune response. Our efforts have focused on cGAS, the metazoan sensor of cytosolic dsDNA, the second messenger cGAMP and the adaptor STING. Our structural studies identified cGAMP, produced by DNA-activated cGAS from GTP and ATP, to be c[G(2',5')pA(3',5')p], that contained an unanticipated 2',5' linkage at the GpA step. Our research was next extended to STING activation by cGAMP and targeting by the anti-viral agent DMXAA [collaborators: Thomas Tuschl (Rockefeller), Winfried Barchet (University Hospital-Bonn) and Roger Jones (Rutgers)].

Wang, Y., et al., Tuschl, T., Hartmann, G. & Patel, D. J. (2010). Structural and functional insights into 5'-ppp-RNA pattern recognition by the innate immune receptor RIG-I. ***Nat. Struct. Mol. Biol.*** 17, 781-787.

Gao, P., et al., Tuschl, T. & Patel, D. J. (2013). Cyclic [G(2',5')pA(3',5')p] is the metazoan second messenger produced by DNA-activated cyclic GMP-AMP synthase. ***Cell*** 153, 1094-1107.

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Lipid Transfer Proteins

Our group initiated a structural biology program on lipid transfer proteins that acquire and release neutral glycosphingolpids and charged phosphosphingolipids during lipid intermembrane transfer and presentation processes. Our studies established the molecular basis underlying differentiation of neutral from charged lipids by their respective head group recognition centers, and defined the alignment of one or both lipid chains within a molded-to-fit hydrophobic tunnel, thereby supporting a cleft-like gating mechanism, whereby lipid chains sequentially entered and departed the tunnel in the membrane-associated state [collaborator: Rhoderick Brown (Hormel Institute); Charles Chalfant (Virginia Commonwealth)].

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Protein-RNA/DNA Complexes on Disease-related Systems

Our group has undertaken x-ray and NMR structural studies on complexes of peptides and proteins bound to their RNA and DNA targets to decipher principles associated with complex formation, as part of an effort towards the eventual formulation of a recognition code mediating protein-RNA complex formation [Collaborators: Thomas Tuschl (Rockefeller); Yang Shi (Harvard Medical School); Robert Darnell (Rockefeller); Eric Lai (MSKCC); Matsuori Inouye (Rutgers); Elisa Izaurralde (Max-Planck-Tubingen)].

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DNA Lesion Architecture and Processing of Damage Sites by Bypass Polymerases

Our studies of the conformation of covalent carcinogenic DNA lesions along DNA have identified groove binding and intercalation-mediated alignments as a function of lesion chirality. We have also addressed the consequences of processing of oxidative, alkylation damage and aromatic amine adducts of guanine in DNA by Dpo4 bypass polymerase. These efforts have yielded mechanistic insights into the translocation mechanics mediated by the bypass polymerase during a cycle of binding and incorporation of nucleoside triphosphates opposite the lesion, as well as the consequences of error-free and error-prone bypass opposite covalent adducts. [collaborators: Suse Broyde and Nicholas Geacintov (New York University)].

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