SCIENCE CHINA
Life Sciences

• NEWS AND VIEWS •

January 2016 Vol.59 No.1: 89–92
doi: 10.1007/s11427-015-4983-4

Base-excision repair and beyond —A short summary attributed to scientific achievements of Tomas Lindahl, Nobel Prize Laureate in Chemistry 2015

Shuangli Mi[1], Arne Klungland[2,3*] & Yun-Gui Yang[1*]

[1]*Key Laboratory of Genomic and Precision Medicine, Collaborative Innovation Center of Genetics and Development, CAS Center for Excellence in Molecular Cell Science, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China;*
[2]*Department of Microbiology, Division of Diagnostics and Intervention, Institute of Clinical Medicine, Oslo University Hospital, Rikshospitalet, Oslo NO-0027, Norway;*
[3]*Department of Molecular Medicine, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway*

Received November 28, 2015; accepted December 7, 2015; published online December 15, 2015

Citation: Mi, S., Klungland, A., and Yang, Y. G. (2016). Base-excision repair and beyond—A short summary attributed to scientific achievements of Tomas Lindahl, Nobel Prize Winner in Chemistry 2015. Sci China Life Sci 59, 89−92. doi: 10.1007/s11427-015-4983-4

Tomas Lindahl contributed his scientific career to unveiling fundamental mechanisms of DNA decay and repair. He made several ground-breaking discoveries on genome instability, novel DNA repair activities and pathways, and disease association.

The 2015 Nobel Prize in Chemistry was awarded jointly to Tomas Lindahl, Paul Modrich and Aziz Sancar for their mechanistic studies of DNA repair. Their findings were affirmed to have "enormous consequences" that have led to insights in cancer treatments.

Tomas Lindahl is an admirable scientist with great achievement on fundamental mechanisms of DNA decay and DNA repair in the fields of cancer therapy, inherited human genetic disorders and ancient DNA. He started his scientific career at Karolinska Institute where he completed his PhD work in 1967. Before he obtained his ground-breaking achievements on DNA repair, Tomas Lindahl had been focusing, also made great discoveries, on Epstein-Barr virus studies in his first research decade. He initially observed non-integrated covalently-closed circles of Epstein-Barr virus genome and pointed out the essentiality of Epstein-Barr virus DNA in cancer cell lines (Adams and Lindahl, 1975; Kaschka-Dierich et al., 1976). He then identified several sequence variants of the Epstein-Barr virus DNA (Rymo et al., 1979). The finding has been surprisingly applied and extended into the cancer progression studies until nowadays (Lee et al., 2015; Liang et al., 2015; Traylen et al., 2015). For instance, Epstein-Barr virus DNA has been used to diagnose chronic lymphocytic leukemia (Liang et al., 2015).

In 1978, Tomas Lindahl became a professor at the University of Gothenburg in Sweden after his postdoctoral training was completed at Princeton University and the Rockefeller University in the USA. Since then, his work was dedicated to characterize and quantify spontaneous endogenous DNA damage and repair (Breimer and Lindahl, 1980; Breimer and Lindahl, 1984, 1985a, 1985b; Chetsanga and Lindahl, 1979; Franklin and Lindahl, 1988; Harris et al., 1983; Karam et al., 1990; Karran and Lindahl, 1980, 1985; Karran et al., 1979; Lehmann et al., 1988; Lindahl, 1972, 1976, 1987, 1990; Lindahl and Wood, 1989; Rydberg and Lindahl, 1982; Teo et al., 1984, 1986; Wood et al., 1988). DNA is the genetic material that carries all of our genetic information and in the early 1970s, it was generally believed to be an extremely stable molecule. This was challenged by Tomas Lindahl's studies. From the 1970s to 1980s, he demonstrated that DNA has limited chemical stability and would decay quickly because of spontaneous changes, radiation, free radicals and carcinogenic substances (Lindahl, 1993). He demonstrated that over thousands of

*Corresponding author (email: arne.klungland@medisin.uio.no; ygyang@big.ac.cn)

potentially mutagenic and cytotoxic changes challenged the DNA on a daily basis in a single human cell. These DNA lesions are generated during the biological processes of hydrolytic depurination, deamination of cytosine residues, oxidation of guanine and pyrimidine residues and methylation of adenine residues to 3-methyladenine etc. (Lindahl, 2013). In order to avoid DNA disintegrating, there must be some DNA repair enzymes and mechanisms that could counteract those amounts of DNA damages. Therefore, Tomas Lindahl started to focus on DNA repair mechanisms since then. He published a very important review "Instability and decay of the primary structure of DNA" in *Nature* in 1993 to discuss DNA damaging and repairing processes (Lindahl, 1993). All the findings of his research have laid the foundation for cancer research and human genetic disorders in present scientific studies (Santos, 2015; Tokarz et al., 2015; Wang, 2015).

Tomas Lindahl's most outstanding contribution to 'The Cell's Toolbox for DNA Repair' was to observe the base excision-repair (BER) pathway, which is an endogenous mechanism responsible for removing small, non-helix-distorting base lesions from the genome and thus repairing the DNA damage (Lindahl, 1979). He also identified several DNA repair enzymes with previously-unknown modes of action in BER (Figure 1), including DNA glycosylases (Figure 1A-I), AP endonucleases (Figure 1A-II), the O^6-methylguanine-DNA methylatransferase (Figure 1B) and the AlkB family of DNA dioxygenases (Figure 1C) (Breimer and Lindahl, 1980, 1985a; Lindahl, 1979; Ljungguist and Lindahl, 1974; Ljungguist et al., 1974, 1975, 1976; Demple et al., 1982; Harris et al., 1983; Karran et al., 1979; McCarthy and Lindahl, 1985; Olsson and Lindahl, 1980; Teo et al., 1984; Duncan et al., 2002; Kolvisto et al., 2003; Sedgwick et al., 2006, 2007 Trewick et al., 2002). The AlkB repair mechanism was later shown to have fundamental importance for histone demethylation, 5-methylC hydroxylation and reversible RNA methylation (Figure 1D) (Jia et al., 2011; Zheng et al., 2013).

In addition, Tomas Lindahl's group characterized two of the major DNA specific exonucleases, TREX1 and FEN1, in mammalian cell nuclei (Figure 1A-III, 1E). TREX1 is a 3′ to 5′ exonuclease and FEN1 is a 5′ to 3′ exonuclease.

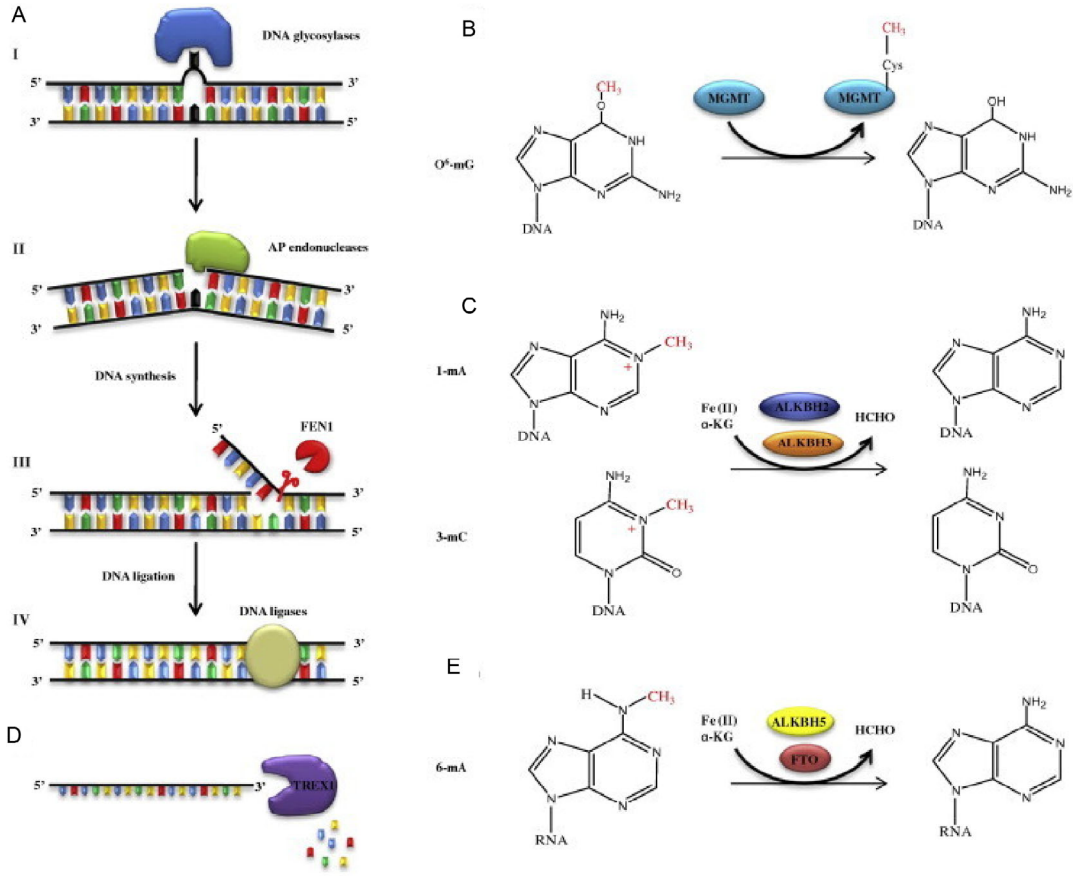

Figure 1 (color online) Overview of mechanistic models for enzymatic reactions (Lindahl, 2013) A, DNA glycosylases catalyze the cleavage of base-sugar bonds (I); AP endonucleases incise double-stranded DNA at base-free sugar-phosphate residues (II); FEN1 removes overhangs and flaps from DNA (III) and eukaryotic DNA ligases ligate DNA ends (IV). B, O^6-methylguanine-DNA methyltransferase (MGMT) irreversibly transfers a promutagenic methyl group from alkylated DNA to a specific cysteine residue in the transferase itself. C, DNA dioxygenases remove certain cytotoxic methyl groups from alkylated base residues by oxidative demethylation in the presence of iron and oxoglutarate. D, FTO and ALKBH5 demethylate RNA m^6A as a novel epigenetic marker in α-ketoglutarate (α-KG) and Fe^{2+}-dependent manner. E, TREX1 is a 3′ to 5′ exonuclease with preference for single-stranded DNA (Courtesy from Lindahl (2013)).

Both are also the DNA repair factors able to remove overhangs and flaps from DNA (Klungland and Lindahl, 1997; Sanderson and Lindahl, 2002). After Tomas Lindahl published his works on TREX1 and FEN1, studies on these two DNA repair factors have been continued. For instance, a form of inherited systemic lupus erythematosus in human cells, called Aicardi-Goutieres syndrome, was found to be caused by the loss of TREX1(Crow et al., 2006). More recent studies showed an accumulation of single-strand DNA and persistent checkpoint activation in TREX1-negative cells (Yang et al., 2007).

Tomas Lindahl completed numerous pioneering works on DNA repair. Many of his collaborators took part in these works. In 1990, together with a senior postdoctoral fellow, Dr. Rick Wood, they established a human cell-free system for ATP-dependent nucleotide excision repair (Hansson et al., 1990). In collaboration with Dr. Lee Johnston, the human DNA ligase I cDNA was cloned and sequenced (Barnes et al., 1990). This enzyme functions in DNA replication and repair. Moreover, in 2001, a complex and chemically-stable oxidative DNA lesion, cyclopurine deoxynucleoside, was identified by Tomas Lindahl and Jean Cadet (Kuraokam et al., 2001). They determined that this DNA lesion could be exclusively repaired by nucleotide excision repair in contrast to other oxidative DNA lesions (Kuraokam et al., 2001). All of these works have a vital elicitation role for the studies in other biological fields.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

Adams, A., and Lindahl, T. (1975). Epstein-Barr Virus genomes with properties of circular DNA molecules in carrier cells. Proc Natl Acad Sci USA 72, 1477–1481.

Barnes, D.E., Johnston, L.H., Kodama, K., Tomkinson, A.E., Lasko, D.D., and Lindahl, T. (1990). Human DNA ligase I cDNA: cloning and functional expression in *Saccharomyces cerevisiae*. Proc Natl Acad Sci USA 87, 6679–6683.

Breimer, L., and Lindahl, T. (1980). A DNA glycosylase from *Escherichia coli* that releases free urea from a polydeoxyribonucleotide containing fragments of base residues. Nucleic Acids Res 8, 6199–6211.

Breimer, L.H., and Lindahl, T. (1984). DNA glycosylase activities for thymine residues damaged by ring saturation, fragmentation, or ring contraction are functions of endonuclease III in *Escherichia coli*. J Biol Chem 259, 5543–5548.

Breimer, L.H., and Lindahl, T. (1985a). Enzymatic excision of DNA bases damaged by exposure to ionizing radiation or oxidizing agents. Mutat Res 150, 85–89.

Breimer, L.H., and Lindahl, T. (1985b). Thymine lesions produced by ionizing radiation in double-stranded DNA. Biochemistry 24, 4018–4022.

Chetsanga, C.J., and Lindahl, T. (1979). Release of 7-methylguanine residues whose imidazole rings have been opened from damaged DNA by a DNA glycosylase from *Escherichia coli*. Nucleic Acids Res 6, 3673–3684.

Crow, Y.J., Hayward, B.E., Parmar, R., Robins, P., Leitch, A., Ali, M., Black, D.N., van Bokhoven, H., Brunner, H.G., Hamel, B.C., Corry, P.C., Cowan, F.M., Frints, S.G., Klepper, J., Livingston, J.H., Lynch, S.A., Massey, R.F., Meritet, J.F., Michaud, J.L., Ponsot, G., Voit, T., Lebon, P., Bonthron, D.T., Jackson, A.P., Barnes, D.E., Lindahl, T. (2006). Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 cause Aicardi-Goutières syndrome at the AGS1 locus. Nat Genet 38, 917–920.

Demple, B., Jacobsson, A., Olsson, M., Robins, P., and Lindahl, T. (1982). Repair of alkylated DNA in *Escherichia coli*. Physical properties of O6-methylguanine-DNA methyltransferase. J Biol Chem 257, 13776–13780.

Duncan, T., Trewick, S.C., Kolvisto, P., Bates, P.A., Lindahl, T., and Sedgwick, B. (2002). Reversal of DNA alkylation damage by two human dioxygenases. Proc Natl Acad Sci USA 99, 16660–16665.

Franklin, W.A., and Lindahl, T. (1988). DNA deoxyribophosphodiesterase. EMBO J, 7, 3617–3622.

Hansson, J., Grossman, L., Lindahl, T., and Wood, R.D. (1990). Complementation of the xeroderma pigmentosum DNA repair synthesis defect with *Escherichia coli* UvrABC proteins in a cell-free system. Nucleic Acids Res 18, 35–40.

Harris, A.L., Karran, P., and Lindahl, T. (1983). O6-Methylguanine-DNA methyltransferase of human lymphoid cells: structural and kinetic properties and absence in repair-deficient cells. Cancer Res 43, 3247–3252.

Jia, G., Fu, Y., Zhao, X.D., Q., Zheng, G., Yang, Y., Yi, C., Lindahl, T., Pan, T., Yang, Y.G., and He, C. (2011). N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol 7, 885–887.

Karam, L.R., Calsou, P., Franklin, W.A., Painter, R.B., Olsson, M., and Lindahl, T. (1990). Modification of deoxyribose-phosphate residues by extracts of ataxia telangiectasia cells. Mutat Res 236, 19–26.

Karran, P., and Lindahl, T. (1980). Hypoxanthine in deoxyribonucleic acid: generation by heat-induced hydrolysis of adenine residues and release in free form by a deoxyribonucleic acid glycosylase from calf thymus. Biochemistry 19, 6005–6011.

Karran, P., and Lindahl, T. (1985). Cellular defence mechanisms against alkylating agents. Cancer Surv 4, 583–599.

Karran, P., Lindahl, T., and Griffin, B. (1979). Adaptive response to alkylating agents involves alteration in situ of O6-methylguanine residues in DNA. Nature 280, 76–77.

Kaschka-Dierich, C., Adams, A., Lindahl, T., Bornkamm, G.W., Bjursell, G., Klein, G., Giovanella, B.C., and Singh, S. (1976). Intracellular forms of Epstein-Barr virus DNA in human tumour cells *in vivo*. Nature 260, 302–306.

Klungland, A., and Lindahl, T. (1997). Second pathway for completion of human DNA base excision-repair: reconstitution with purified proteins and requirement for DNase IV (FEN1). EMBO J 16, 3341–3348.

Kolvisto, P., Duncan, T., Lindahl, T., and Sedgwick, B. (2003). Minimal methylated substrate and extended substrate range of *Escherichia coli* AlkB protein, a 1-methyladenine-DNA dioxygenase. J Biol Chem 278, 44348–44354.

Kuraokam, I., Robins, P., Masutani, C., Hanaoka, F., Gasparutto, D., Cadet, J., Wood, R.D., and Lindahl, T. (2001). Oxygen free radical damage to DNA. Translesion synthesis by human DNA polymerase eta and resistance to exonuclease action at cyclopurine deoxynucleoside residues. J Biol Chem 276, 49283–49288.

Lee, V.H., Kwong, D.L., Leung, T.W., Choi, C.W., Lam, K.O., Sze, C.K., Ho, P., Chan, W.L., Wong, L.S., and Leung, D. (2015). Post-radiation plasma Epstein-Barr virus DNA and local clinical remission after radical intensity-modulated radiation therapy for nasopharyngeal carcinoma. Clin Oncol doi: 10.1016/j.clon.2015.09.009

Lehmann, A.R., Willis, A.E., Broughton, B.C., James, M.R., Steingrimsdottir, H., Harcourt, S.A., Arlett, C.F., and Lindahl, T. (1988). Relation between the human fibroblast strain 46BR and cell lines representative of Bloom's syndrome. Cancer Res 48, 6343–6347.

Liang, J.H., Gao, R., Xia, Y., Gale, R.P., Chen, R.Z., Yang, Y.Q., Wang, L., Qu, X.Y., Qiu, H.R., Cao, L., Hong, M., Wang, R., Wang, Y., Fan, L., Chen, Y.Y., Hu, Z.B., Li, J.Y., and Xu, W. (2015). Prognostic impact of Epstein-Barr Virus (EBV)-DNA copy number at diagnosis in chronic lymphocytic leukemia. Oncotarget doi: 10.18632/oncotarget.6281

Lindahl, T. (1972). Mammalian deoxyribonucleases acting on damaged

DNA. Johns Hopkins Med J Suppl 1, 3–13.
Lindahl, T. (1976). New class of enzymes acting on damaged DNA. Nature, 259, 64–66.
Lindahl, T. (1979). DNA glycosylases, endonucleases for apurinic/apyrimidinic sites, and base excision-repair. Prog Nucleic Acid Res Mol Biol 22, 135–192.
Lindahl, T. (1987). The 1987 Walter Hubert lecture. Regulation and deficiencies in DNA repair. Br J Cancer 56, 91–95.
Lindahl, T. (1990). Repair of intrinsic DNA lesions. Mutat Re 238, 305–311.
Lindahl, T. (1993). Instability and decay of the primary structure of DNA. Nature 362, 709–715.
Lindahl, T. (2013). My Journey to DNA Repair. Genomics Proteomics Bioinformatics 11, 2–7.
Lindahl, T., and Wood, R.D. (1989). DNA repair and recombination. Curr Opin Cell Biol, 1, 475–480.
Ljungguist, S., Andersson, A., and Lindahl, T. (1974). A mammalian endonuclease specific for apurinic sites in double-stranded deoxyribonucleic acid. II. Further studies on the substrate specificity. J Biol Chem 249, 1536–1540.
Ljungguist, S., and Lindahl, T. (1974). A mammalian endonuclease specific for apurinic sites in double-stranded deoxyribonucleic acid. I. Purification and general properties. J Biol Chem 249, 1530–1535.
Ljungguist, S., Lindahl, T., and Howard-Flanders, P. (1976). Methyl methane sulfonate-sensitive mutant of *Escherichia coli* deficient in an endonuclease specific for apurinic sites in deoxyribonucleic acid. J Bacteriol 126, 646–653.
Ljungguist, S., Nyberg, B., and Lindahl, T. (1975). Mammalian DNA endonuclease acting at apurinic sites: absence of associated exonuclease activity. FEBS Lett 57, 169–171.
McCarthy, T.V., and Lindahl, T. (1985). Methyl phosphotriesters in alkylated DNA are repaired by the Ada regulatory protein of *E. coli*. Nucleic Acids Res 13, 2683–2698.
Olsson, M., and Lindahl, T. (1980). Repair of alkylated DNA in Escherichia coli. Methyl group transfer from O6-methylguanine to a protein cysteine residue. J Biol Chem, 255, 10569–10571.
Rydberg, B., and Lindahl, T. (1982). Nonenzymatic methylation of DNA by the intracellular methyl group donor S-adenosyl-L-methionine is a potentially mutagenic reaction. EMBO J 1, 211–216.
Rymo, L., Lindahl, T., and Adams, A. (1979). Sites of sequence variability in Epstein-Barr virus DNA from different sources. Proc Natl Acad Sci USA 76, 2794–2798.
Sanderson, R.J., and Lindahl, T. (2002). Down-regulation of DNA repair synthesis at DNA single-strand interruptions in poly(ADP-ribose) polymerase-1 deficient murine cell extracts. DNA Repair, 1, 547–558.
Santos, J.C. (2015). Epigenetic regulation of DNA repair machinery in Helicobacter pylori-induced gastric carcinogenesis. World J Gastroenterol 21, 9021–9037.
Sedgwick, B., Robins, P., and Lindahl, T. (2006). Direct removal of alkylation damage from DNA by AlkB and related DNA dioxygenases. Methods Enzymol 408, 108–120.
Sedgwick, B., Bates, P.A., Paik, J., Jacobs, S.C., and Lindahl, T. (2007). Repair of alkylated DNA: recent advances. DNA Repair, 6, 429–442.
Teo, I., Sedgwick, B., Demple, B., Li, B., and Lindahl, T. (1984). Induction of resistance to alkylating agents in *E. coli*: the ada+ gene product serves both as a regulatory protein and as an enzyme for repair of mutagenic damage. EMBO J 3, 2151–2157.
Teo, I., Sedgwick, B., Kilpatrick, M.W., McCarthy, T.V., and Lindahl, T. (1986). The intracellular signal for induction of resistance to alkylating agents in *E. coli*. Cell 45, 315–324.
Tokarz, P., Blasiak, J., and Kaarniranta, K. (2015). Role of the cell cycle re-initiation in DNA damage response of postmitotic cells and its implication in the pathogenesis of neurodegenerative diseases. Rejuvenation Res. Jul 27
Traylen, C., Ramasubramanyan, S., Zuo, J., Rowe, M., Almohannad, R., Heesom, K., Sweet S.M., Matthews D.A., and Sinclair, A.J. (2015). Identification of Epstein-Barr Virus Replication Proteins in Burkitt's Lymphoma Cells. Pathogens 4, 739–751.
Trewick, S.C., Henshaw, T.F., Hausinger, R.P., Lindahl, T., and Sedgwick, B. (2002). Oxidative demethylation by *Escherichia coli* AlkB directly reverts DNA base damage. Nature 419, 174-178.
Wang, Q.E. (2015). DNA damage responses in cancer stem cells: Implications for cancer therapeutic strategies. World J Biol Chem 6, 57-64.
Wood, R.D., Robins, P., and Lindahl, T. (1988). Complementation of the xeroderma pigmentosum DNA repair defect in cell-free extracts. Cell 53, 97–106.
Yang, Y.G., Lindahl, T., and Barnes, D.E. (2007). Trex1 exonuclease degrades ssDNA to prevent chronic checkpoint activation and autoimmune disease. Cell 131, 873–886.
Zheng, G., Dahl, J.A., Niu, Y., Fedorcsak, P., Huang, C.M., Li, C.J., Vågbø, C.B., Shi, Y., Wang, W.L., Song, S.H., Lu, Z., Bosmans, R.P., Dai, Q., Hao, Y.J., Yang, X., Zhao, W.M., Tong, W.M., Wang, X.J., Bogdan, F., Furu, K., Fu, Y., Jia, G., Zhao, X., Liu, J., Krokan, H.E., Klungland, A., Yang, Y.G., and He, C. (2013). ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. Mol Cell 49, 18–29