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LIFE-TIME ACHIEVEMENT REVIEW

My Journey to DNA Repair

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Abstract I completed my medical studies at the Karolinska Institute in Stockholm but have always been devoted to basic research. My longstanding interest is to understand fundamental DNA repair mechanisms in the fields of cancer therapy, inherited human genetic disorders and ancient DNA. I initially measured DNA decay, including rates of base loss and cytosine deamination. I have discovered several important DNA repair proteins and determined their mechanisms of action. The discovery of uracil-DNA glycosylase defined a new category of repair enzymes with each specialized for different types of DNA damage. The base excision repair pathway was first reconstituted with human proteins in my group. Cell-free analysis for mammalian nucleotide excision repair of DNA was also developed in my laboratory. I found multiple distinct DNA ligases in mammalian cells, and led the first genetic and biochemical work on DNA ligases I, III and IV. I discovered the mammalian exonucleases DNase III (TREX1) and IV (FEN1). Interestingly, expression of TREX1 was altered in some human autoimmune diseases. I also showed that the mutagenic DNA adduct O^6-methylguanine (O^6mG) is repaired without removing the guanine from DNA, identifying a surprising mechanism by which the methyl group is transferred to a residue in the repair protein itself. A further novel process of DNA repair discovered by my research group is the action of AlkB as an iron-dependent enzyme carrying out oxidative demethylation.

In my early research career, I observed that Epstein-Barr virus DNA is present as nonintegrated covalently-closed circles, as well as integrated viral DNA fragments, in virus-transformed cells from Burkitt lymphoma and nasopharyngeal carcinoma patients in 1975/1976 [1–23]. This work was surprising because it preceded similar studies on papilloma virus in other laboratories.

A main achievement has been to characterize and quantify spontaneous, endogenously-produced DNA damage during the 1970s and 1980s [24–44]. Surprisingly, main events, such as hydrolytic depurination, deamination of cytosine residues, oxidation of guanine and pyrimidine residues and methylation of adenine residues to 3-methyladenine, amount to 10,000 potentially mutagenic and cytotoxic changes per day in a human genome. These results strongly indicate that special DNA repair enzymes and mechanisms must exist to counteract endogenous DNA damage.

I thus became enthusiastic about understanding fundamental DNA repair mechanisms (**Figure 1**). A review of my work on endogenous DNA damage and its repair was published in Nature [45]. I discovered the base excision-repair pathway, the major cellular defense against endogenous DNA damage [46–57]. Later on, the two variants of base excision repair

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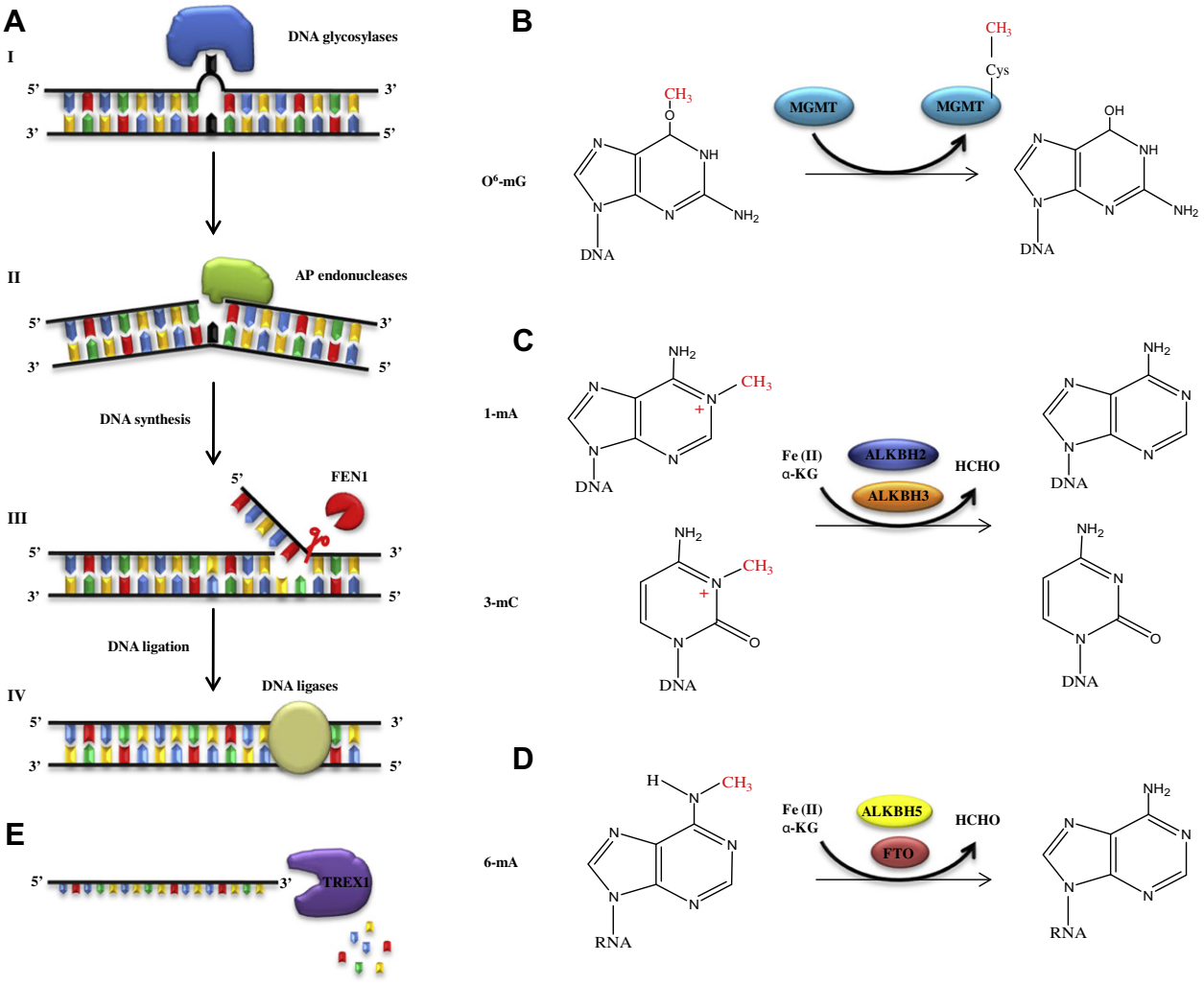

Figure 1 Overview of mechanistic models for enzymatic reactions

A. (**I**) DNA glycosylases catalyze the cleavage of base-sugar bonds; (**II**) AP endonucleases incise double-stranded DNA at base-free sugar-phosphate residues; (**III**) FEN1 removes overhangs and flaps from DNA and (**IV**) eukaryotic DNA ligases ligate DNA ends. **B.** O^6-methylguanine-DNA methyltransferase (MGMT) transfers irreversibly 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.

(short-patch *vs* long-patch repair) were reconstituted with purified proteins. I unveiled several DNA repair enzymes of previously-unknown modes of action, including (i) DNA glycosylases that catalyze the cleavage of base-sugar bonds (uracil-DNA glycosylase) [58–67], 3-methyladenine–DNA glycosylase [68–70] and DNA glycosylases that release oxidised base residues (Figure 1A-I) [29,35]; (ii) AP endonucleases that incise double-stranded DNA at base-free sugar-phosphate residues (in parallel with Prof. Walter Verly) (Figure 1A-II) [46,71–75]; (iii) the O^6-methylguanine-DNA methyltransferase (MGMT, Ada protein that transfers irreversibly a promutagenic methyl group from alkylated DNA to a specific cysteine residue in the transferase itself) (Figure 1B) [27,31,32,76–83]; (iv) DNA dioxygenases (AlkB protein and its homologs) that remove certain cytotoxic methyl groups from alkylated base residues by oxidative demethylation in the presence of iron and oxoglutarate (together with Dr Barbara Sedgwick and Prof. Erling Seeberg) (Figure 1C) [84–89]. This DNA repair mechanism also resulted in the discovery of new group of enzymes FTO and ALKBH5 that demethylate a novel epigenetic marker RNA m^6A (Figure 1D) [90,91].

It is worth mentioning that I found a complex and chemically-stable oxidative DNA lesion, cyclopurine deoxynucleoside, which is exclusively repaired by nucleotide excision repair in contrast to other oxidative DNA lesions (in collaboration with Prof. Jean Cadet) [92]. Moreover, I established a human cell-free system for ATP-dependent nucleotide excision repair (together with a senior postdoctoral fellow, Dr Rick Wood) [93]. This assay system allowed for purification of proteins such as XPA, which is missing in repair-defective xeroderma pigmentosum (XP) cells, by *in vitro* complementation.

It was interesting for me to identify and characterize the DNA ligases in eukaryotic cells, which require ATP rather that NAD as cofactor, in contrast to most bacterial ligases

(Figure 1A-IV) [94–96]. The main DNA ligases that function in mammalian cells include DNA ligase I (DNA replication and repair) [97,98], DNA ligase III (base excision repair) [62] and DNA ligase IV (non-homologous end joining) [99–101]. The human DNA ligase I cDNA was cloned and sequenced in 1990 (in collaboration with Dr Lee Johnston) [102], which allowed for the localization of the active site for enzyme-adenylate complex formation. Early observations on alterations of DNA ligase I in human diseases prior to that year were only partially confirmed.

Furthermore, I discovered and characterized the two major DNA-specific exonucleases in mammalian cell nuclei, originally termed DNase III and IV, now called TREX1 and FEN1 (Figure 1A-III, 1E) [55], respectively. The FEN1 enzyme was shown to be a 5' to 3'exonuclease, a replication and repair factor that removes overhangs and flaps from DNA (in parallel with Dr Michael Lieber) [55,103]. TREX1 was shown to be a 3' to 5' exonuclease with preference for single-stranded DNA. More recent studies established that loss of TREX1 in human cells results in a form of inherited systemic lupus erythematosus (SLE) called Aicardi-Goutières syndrome (AGS) (in collaboration with Dr Yanick Crow) [92,104–106]. In 2007, TREX1-negative cells were shown to accumulate single-stranded DNA and exhibit persistent checkpoint activation (together with coworkers, Drs Yun-Gui Yang and Deborah Barnes) [107].

Besides my discovery of several DNA repair enzymes, I also observed that self-methylation of the Ada protein [27,32,37,80–83,108], with methylation of a cysteine residue within the regulatory domain, as a consequence of DNA phosphotriester repair, converts Ada to a transcription factor. This work, published in 1986, was the first example of activation of a transcription factor by a posttranslational modification event.

Beyond my own scientific research, I also spent time to manage research laboratories, and still provide advice for their individual research concepts and directions. As the former director of the Clare Hall Laboratories at ICRF and Cancer Research UK, I was pleased to see that Clare Hall Laboratories became an internationally-renowned center of research into DNA processing. I am also very glad to see that many of my former colleagues succeed in their academic careers.

I still enjoy very much doing science. It is pleasure, it is very interesting and it is stimulating. It changes all the time. I would like to be here around hundred years to see how science develops.

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Dr. Tomas Lindahl completed medical studies at the Karolinska Institute in Stockholm but has always been devoted to research. He worked on nucleic acid biochemistry with Jacques Fresco at Princeton and Gerald Edelman at Rockefeller University, and joined the faculty of the Karolinska Institute in 1969. He became Professor at the University of Gothenburg in 1978. In 1981 he was appointed Head of the Mutagenesis Laboratory at the ICRF Mill Hill Laboratories in London. From 1984 to 2006, he was Director of the Clare Hall Laboratories at ICRF and Cancer Research UK, also serving as Deputy Director of Research. Dr. Lindahl's contributions to understanding DNA repair are fundamental and have long-lasting impact in the fields of cancer therapy, inherited human genetic disorders and ancient DNA. Beyond his own outstanding scientific achievements, his stewardship established Clare Hall Laboratories as an internationally-renowned center of research into DNA processing. The success of colleagues working together with him is a measure of his insight, support and leadership. Amongst many prestigious honours, Dr. Lindahl is a member of EMBO, a fellow of the Royal Swedish Academy of Sciences and the Royal Society. He delivered the Royal Society Croonian Lecture in 1996. Dr. Lindahl received a Royal Medal in 2007 and the prestigious Copley Medal of the Royal Society in 2010.