BASE EXCISION REPAIR OF DNA

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INTRODUCTION

The terms base excision repair (BER) and nucleotide excision repair (NER) were first suggested by Duncan et al in 1976 (1), since at that time distinct modes of excision repair appeared distinguishable by at least two criteria.

(i) In BER, damaged or inappropriate bases are excised as free bases, while in NER such bases are excised as part of nucleotides or oligonucleotide sequences.

(ii) Mechanistically there is good evidence that BER involves hydrolysis of glycosylic bonds linking bases to the deoxyribose-phosphate backbone of DNA, as a primary enzymatic event during excision repair (2,3). On the other hand, NER is thought to involve hydrolysis of phosphodiester bonds adjacent to sites of base damage, as a primary enzymatic event. The prototypic example of NER that until recently fulfilled both of these criteria is the excision of pyrimidine dimers from UV-irradiated DNA (4). However, very recent studies from a number of laboratories indicate that at least in M. luteus (5,6) and in phage T4-infected E. coli (7-10), the excision of these lesions requires the action of a specific DNA glycosylase that catalyzes the hydrolysis of the 5' N-glycosylic bond of dimerized pyrimidines. Phosphodiester bonds associated with the resulting apyrimidinic sites are attacked secondarily by one or more AP (apurinic/apyrimidinic) endonucleases, creating nicks in the DNA 5' with respect to the dimers (see article by Grossman, this volume). At present, there is no evidence of which I am aware that this 2-step mechanism for the incision...
of UV-irradiated DNA is more general than the two specific examples just cited. Furthermore, direct analysis of the products of excision catalyzed by the combined action of the T4 enzyme activity and E. coli DNA polymerase I in vitro has demonstrated that pyrimidine dimers are excised as part of an oligonucleotide structure (11). For the purposes of this discussion I define BER only in terms of criterion (i) mentioned above, viz., the structure of the excised product. By this definition therefore the excision of pyrimidine dimers, whether involving the action of a

Figure 1 - Diagrammatic representation of base excision repair showing a) DNA glycosylase catalyzed excision of a damaged or inappropriate base (in black), b) AP endonuclease-catalyzed hydrolysis of a phosphodiester bond 5' with respect to a site of base loss, c) excision of the deoxyribose-phosphate residue as part of an oligonucleotide by degradation of the DNA at the site of AP endonuclease-catalyzed incision, d) repair synthesis and DNA ligation. The insertion pathway is designated as e). The nucleotide excision pathway showing endonuclease-catalyzed incision of DNA 5' to a model dinucleotide lesion (e.g., pyrimidine dimer) is shown for comparison.