



**HAL**  
open science

# UV-induced formation of DNA damage in cells and their mutational consequences

Thierry Douki, S Adar

► **To cite this version:**

Thierry Douki, S Adar. UV-induced formation of DNA damage in cells and their mutational consequences. Roberto Improtà; Thierry Douki. DNA Photodamage: From Light Absorption to Cellular Responses and Skin Cancer, Royal Society of Chemistry, 2021, Comprehensive Series in Photochemical & Photobiological Sciences, 978-1-83916-196-4. 10.1039/9781839165580-00133 . hal-03689535

**HAL Id: hal-03689535**

**<https://hal.science/hal-03689535>**

Submitted on 7 Jun 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



15 ABSTRACT

16 Ultraviolet radiation induces a wide variety of damage in DNA that can originate from  
17 either photochemical reaction triggered by absorption of photons by DNA bases or  
18 oxidation processes mostly induced by photosensitization. The nature of DNA damage  
19 is dependent of numerous factors such the wavelength, the sequence, the chromatin  
20 structure or the cell type. The present chapter provides a summary of the available  
21 quantitative information of the yield of UV-induced DNA damage as well as the most  
22 recent pieces of information bases on state-of-the-art techniques such as next  
23 generation sequencing. The mutational consequences of the DNA photoproducts are  
24 briefly discussed.

25

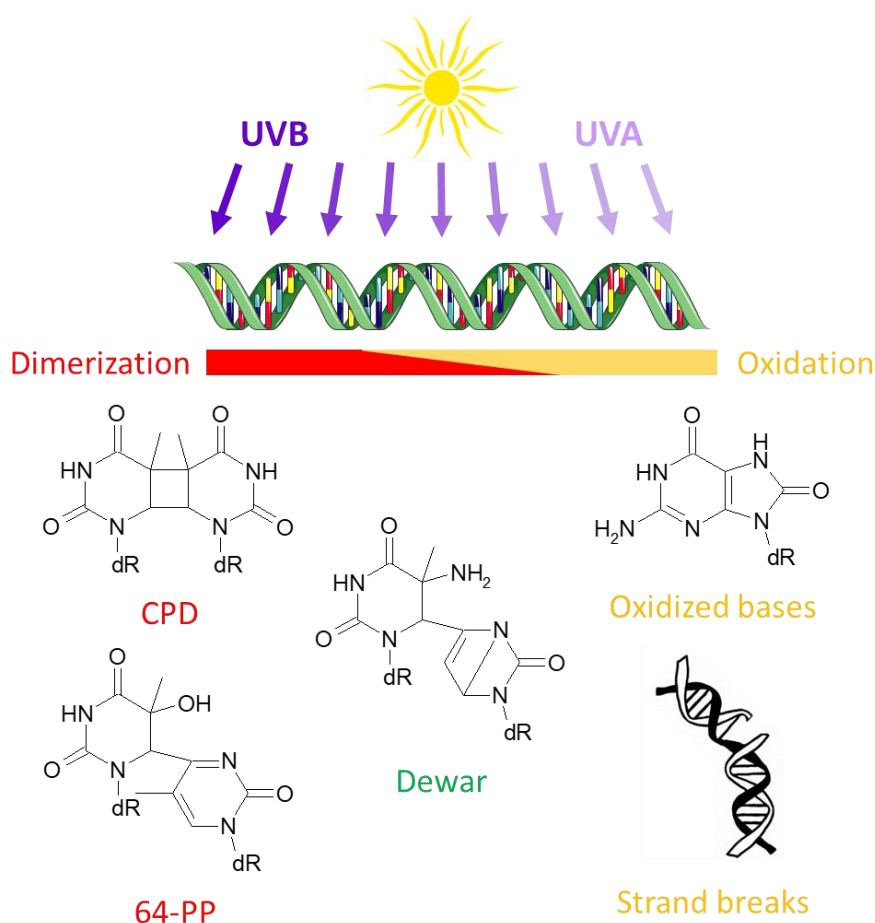
26	Table of Contents	
27	Chapter 7: UV-induced formation of DNA damage in cells and their mutational	
28	consequences. ....	1
29	7.1 Introduction.....	5
30	7.2 UV-induced pyrimidine dimers in cellular DNA .....	6
31	7.2.1 Wavelength-dependent formation of pyrimidine dimers by UVB .....	7
32	7.2.1.1 CPDs and UVB radiation .....	7
33	7.2.1.2 Distribution of pyrimidine dimers in UVB irradiated cells.....	7
34	7.2.2 UVA-induced CPDs.....	9
35	7.2.2.1 Direct formation of CPD upon exposure to UVA.....	9
36	7.2.2.2 Dark CPDs.....	11
37	7.2.3 UVC-induced DNA damage .....	12
38	7.2.3.1 Interest of UVC in photobiology.....	12
39	7.2.3.2 DNA damage in the UVC range.....	12
40	7.2.3.3 Photochemistry in bacterial spores .....	14
41	7.3 Oxidatively generated DNA damage in cells.....	15
42	7.3.1 UVB and oxidative stress .....	15
43	7.3.2 Main UVA-induced photooxidation pathways .....	15
44	7.3.2.1 One-electron oxidation reactions .....	16
45	7.3.2.2 Singlet oxygen .....	16
46	7.3.2.3 Reactive oxygen species arising from the superoxide anion radical..	17
47	7.3.3. Oxidatively generated DNA damage in UVA-irradiated cells.....	18
48	7.4 Spectral composition and photoproduct distribution .....	19
49	7.4.1 Formation of Dewar valence isomers.....	20
50	7.4.2. UV-induced formation of sensitizers.....	21
51	7.4.3. Impact of UVA on the repair of UVB-induced dimers.....	21

52	7.5	DNA damage at the nucleotide resolution in cellular DNA.....	22
53	7.6	UV-induced DNA damage in skin .....	26
54	7.6.1	Yield of lesions in skin .....	27
55	7.6.2	Effect of phototype on the formation of CPDs .....	28
56	7.7	Mutagenic consequences of DNA photodamage.....	29
57	7.7.1.	<i>In vitro</i> data of UV-induced mutagenesis.....	29
58	7.7.2.	Next generation sequencing of human tumours.....	31
59		Abbreviations :.....	33
60		References .....	33
61			
62			
63			

## 64 7.1 Introduction

65 Information gathered over the years in model systems and isolated DNA made possible  
66 the identification the most relevant types of DNA damage that could be generated in  
67 cells upon exposure to UV radiation. They are either dimeric photoproducts involving  
68 adjacent pyrimidine bases or oxidatively generated lesions such as strand breaks and  
69 oxidized bases (Fig. 7.1). In the early 1960's, radioactivity-based assays were  
70 developed to quantify thymine-containing cyclobutane pyrimidine dimers (CPDs). The  
71 subsequent development of immunoassays made possible the collection of large  
72 amounts of information in various cellular systems and in skin not only on CPDs but  
73 also on pyrimidine (6-4) photoproducts (64-PPs) and their Dewar valence isomers  
74 (Dewars) <sup>1,2</sup>. More specific methods based on molecular biology approaches <sup>3</sup> or mass  
75 spectrometry detection <sup>4</sup> provided data on the individual formation of each dimer at the  
76 different bipyrimidine sites. In the recent years, the breakthrough made in next  
77 generation sequencing provided an unprecedented picture on the formation and repair  
78 of DNA in the different region of chromatin <sup>5,6</sup>. Information on oxidatively generated  
79 lesions was mostly obtained through electrophoretic-based assay such as the comet  
80 assay <sup>7</sup> or alkaline elution <sup>8</sup>. These methods were primarily developed for the  
81 quantification of strand breaks but could be extended to damaged bases by the use of  
82 purified DNA *N*-glycosylases that recognize well-defined classes of damage. Some  
83 specific lesions like 8-oxo-7,8-dihydroguanine (8-oxoGua) were also quantified by  
84 chromatographic approaches. The purpose of this chapter is to combine all these  
85 pieces of information, with emphasis placed on the most recent results but without  
86 neglecting relevant earlier data, in order to provide insight into the distribution of the  
87 most frequent UV-induced damage. Factors such as the cell type, the spectrum of the  
88 incident light and the specificity of the formation of damage in skin are also discussed.

89 Last, a short overview of link between DNA damage and mutagenesis is provided,  
 90 especially in the light of recent next generation sequencing data.



91  
 92 *Figure 7.1: Chemical structure of the main DNA damage induced by UV radiation.*  
 93 *UVB mostly leads to the formation of pyrimidine dimers while UVA is at the origin of a*  
 94 *strong oxidative stress. However, as discussed in the present chapter, the boundary*  
 95 *between the two wavelengths ranges is less tight that long believed.*

## 96 7.2 UV-induced pyrimidine dimers in cellular DNA

97 UV radiation is an efficient DNA damaging agent but the yield and the nature of the  
 98 photodamage strongly depend on the wavelength of the incident photons. Major  
 99 attention has been paid to the UVA (320-400 nm) and UVB ranges (280-320 nm),  
 100 which represent more than 95% and less than 5% of solar UV, respectively. Information  
 101 is also available on the DNA damaging effects of UVC light (100-280 nm), which is  
 102 closer to the UV absorption maximum of DNA at 260 nm.

## 103 **7.2.1 Wavelength-dependent formation of pyrimidine dimers by UVB**

### 104 **7.2.1.1 CPDs and UVB radiation**

105 The most efficient portion of the solar spectrum for the induction of pyrimidine dimers  
106 is UVB. This is easily explained by the fact that the wavelength of the most energetic  
107 photons in solar UV is closer to the maximal absorption of DNA (260 nm).  
108 Consequently, DNA base may absorb these photons and reach excited states, thereby  
109 opening the way to photochemical reaction as addressed by Martinez-Fernandez and  
110 Improta in chapter 2 of this volume. Numerous data are available for CPDs. In cultured  
111 cells, the reported yields for broadband UVB lamps varies from 0.01 to 0.06 CPD/10<sup>5</sup>  
112 bases per J/m<sup>2</sup> <sup>9-12</sup>. The differences between these values can be explained by both  
113 the use of different analytical tools, the cell type and the emission spectrum of the UVB  
114 sources. The latter point is a major issue because the yield of the pyrimidine dimers  
115 varies along the UVB range. Action spectra in cultured human fibroblasts <sup>13</sup> show that  
116 the yield of CPD is in a 1 / 0.4 / 0.06 ratio at 280, 290 and 300 nm, respectively. In  
117 CHO cells, ratio of 1 / 0.22 / 0.01 were determined for the yield of CPD at 290, 300 and  
118 310 nm <sup>8</sup>. These values show that the slightest increase in wavelength leads to a  
119 significant decrease in the yield of CPDs. They explain the difference in DNA damaging  
120 properties of sunlight depending on the hour the day, the latitude and the longitude.  
121 When the intensity on the UV radiation decreases as the result of the filter effect of the  
122 atmosphere, the ratio between the intensities of UVB and UVA is reduced <sup>14, 15</sup>.  
123 Differences in emission spectra is also of utmost importance when comparing results  
124 obtained by different teams using different irradiator.

### 125 **7.2.1.2 Distribution of pyrimidine dimers in UVB irradiated cells**



126 Most of the data discussed above are related to CPDs measured as a whole by  
127 immunoassays or to the sole TT CPD quantified by specific techniques. Yet, work on  
128 model systems and isolated DNA has shown that CPDs are formed at the four  
129 bipyrimidine sequences <sup>4, 16</sup>. These works also showed that, because of steric  
130 constraints, only the *cis,syn* diastereoisomer of CPD is detected in double-stranded  
131 DNA while other derivatives are produced in dinucleoside monophosphates and single-  
132 stranded DNA. Similar observations were made in cells with the following decreasing  
133 order of frequency for the *cis,syn* CPD: TT > TC > CT > CC <sup>10, 17-25</sup>. The ratio between  
134 the yields of these CPDs is 10 / 5 / 3 / 1, respectively. 64-PPs are also produced in  
135 significant amount by UVB radiation, although in a 3 to 5 lower yield than CPDs <sup>9, 10, 12,</sup>  
136 <sup>26</sup>. In UVB-irradiated cultured cells, they are formed in detectable amounts only at TT  
137 and TC sites in a 1 to 5 ratio <sup>9, 10, 21, 22, 24, 27</sup>. CT and CC 64-PPs <sup>21</sup> have been detected  
138 in small amounts only upon UVC-irradiation of isolated DNA. The ratio between CPD  
139 and 64-PP is also dependent on the involved pyrimidine bases, with an approximate  
140 ratio of 10 at TT and 1 at TC sites. The ratio between all these different bipyrimidine  
141 photoproducts is constant from one mammalian cell type to the other. This reflects that  
142 the photochemistry of DNA is hardly modulated by the cellular environment. As detailed  
143 below, recent works based on the detection of pyrimidine dimers at the nucleotide  
144 resolution by next generation sequencing led to similar results <sup>6, 28-31</sup>.

145 The only parameter that was found to drastically affect the mean distribution of CPDs  
146 in cells is the GC content of DNA <sup>32</sup>. This mostly concerns bacteria since all eukaryotic  
147 cells exhibit similar proportions of G/C and A/T bases pairs. Interestingly, this study of  
148 the impact of the GC content of DNA on the formation of pyrimidine dimers led to the  
149 conclusion that TC rather than TT dinucleotides are the most reactive sites in DNA. On  
150 a local scale, the reactivity of bipyrimidine sites can be modulated by the methylation

151 of cytosine, an important epigenetic event. Evidence are accumulating for an increased  
152 formation of damage at methylated CpG island <sup>33</sup>, which is associated with increased  
153 mutagenesis <sup>17, 23, 34, 35</sup>.

154 It may be mentioned than UVB may also trigger a secondary photoreaction within 64-  
155 PPs: the conversion into a Dewar valence isomer of the pyrimidone ring <sup>36-39</sup>. This has  
156 been well documented in model systems but is observed in very low yield in cells  
157 exposed to biologically relevant doses of UVB. As discussed later in this chapter,  
158 formation of Dewar in cells requires both UVB and UVA. Another important secondary  
159 reaction is the hydrolytic deamination of cytosine moieties in CPDs and CT and CC  
160 64-PPs and Dewars <sup>40-42</sup>. This process leads to the formation of uracil-containing CPDs  
161 that play a role in mutagenesis, which is dominated by C→T mutations at bipyrimidic  
162 sites as discussed later in this chapter. More information on this process can be found  
163 in chapter 8 by Taylor and colleagues in this book.

## 164 7.2.2 UVA-induced CPDs

### 165 7.2.2.1 Direct formation of CPD upon exposure to UVA

166 Formation of CPDs is not only induced by UVB but also by the less energetic UVA.  
167 This photoreaction has long been neglected because UVA radiation was thought not  
168 to be absorbed by DNA. Yet, precise spectroscopic studies showed that DNA was  
169 actually a chromophore for UVA with an absorption at 350 nm respectively  $10^4$  and  $10^3$   
170 times lower than at 280 and 300 nm <sup>43</sup>. Formation of CPDs in cellular DNA upon  
171 exposure to UVA has first been reported in bacteria <sup>44</sup>. Since then, similar results were  
172 obtained in cultured rodent cells <sup>8, 12, 45, 46</sup> as well as in human fibroblasts <sup>47</sup>,  
173 keratinocytes <sup>22, 48</sup> and melanocytes <sup>49</sup>. The same observation was made in whole  
174 human skin both *in vivo* <sup>50</sup> and *ex vivo* <sup>22, 24, 51</sup>. The ratio between the yield of CPDs

175 after exposure to UVB or UVA is in the same range than the difference in absorption  
 176 (Table 7.1). This value differs from one work to the other, which can be explained by  
 177 differences in emission spectra of the UV sources. The importance of this parameter  
 178 is clearly illustrated in action spectra where values of 60 were found between the ratio  
 179 at 365 nm compared to either 290 nm or 310 nm in CHO cells <sup>8</sup>. Similarly, a ratio of 6  
 180 was determined for the yield of CPD in keratinocytes exposed at 302 nm compared to  
 181 either 365 or 334 nm <sup>47</sup>. The correlation between the yield of CPDs and the DNA  
 182 absorption, combined with the observation of CPD in UVA-irradiated isolated DNA,  
 183 strongly suggests that a direct photochemical rather than a photosensitized process is  
 184 involved in the UVA-induction of CPD <sup>12, 52-54</sup>. A last worth mentioning feature of the  
 185 UVA photochemistry of DNA is that 64-PPs are at the best minor photoproducts. This  
 186 can be explained by the change in the nature of the excited states generated when the  
 187 wavelength of the absorbed photons increases from UVB to UVA <sup>55</sup>.

188 *Table 7.1: Comparison of the induction of CPDs in various cell types exposed to UVB*  
 189 *and UVA radiations. The reported results are the ratio between the yields of*  
 190 *formation.*

Cell type	UV sources*	ratio	ref
CHO cells	290 vs 365 nm 310 vs 365 nm	40000 700	8
CHO cells	bb-UVB vs bb- UVA	700	12
CHO cells	bb-UVB vs bb- UVA	2000	46
Human skin fibroblasts	302 vs 334 nm 302 vs 365 nm	150 1000	47
Human keratinocytes	bb-UVB vs bb- UVA	20000	9
Human skin explants	bb-UVB vs bb- UVA	6500	22
Human skin explants phototype IV Human skin explants phototype II	bb-UVB vs bb- UVA	1100 1050	24

191 \*bb: broadband

## 192 7.2.2.2 Dark CPDs

193 In addition to the formation of CPDs resulting from the weak but real absorption of UVA  
194 photons by DNA, UVA was reported to trigger a delayed formation of CPDs. This  
195 phenomenon was first reported in cultured melanocytes<sup>56</sup> and further extended to  
196 keratinocytes<sup>57</sup>. In both cell types, an oxidative pathway seems to be involved as  
197 shown by the inhibiting effects of antioxidants. Mechanistic studies have been  
198 performed in melanocytes. In this cell type UVA, and to a lesser extent UVB, were  
199 found to induce the formation of dark CPDs in the hours following irradiation of  
200 pigmented melanocytes but not of melanocytes originating from albino mice<sup>56</sup>.  
201 Interestingly, not only TT but also the mutagenic TC and CT CPDs were formed by this  
202 delayed mechanism. Evidence for a role of oxidation products of melanin and melanin  
203 precursor was provided by the replication of this effect on model systems involving  
204 oxidizing species, melanin derivatives and isolated DNA. A proposed mechanism is  
205 thus the formation of endoperoxide by UVA-induced oxidative stress that would then  
206 decompose into excited ketones. Such a mechanism has been previously described  
207 for oxidatively generated lesions<sup>58</sup>. It could induce the formation of CPDs by triplet  
208 energy transfer if the energy of the excited ketone is large enough. This pathway  
209 remains yet to be completely established in order to explain why C-containing dark  
210 CPDs are produced in significant amounts while photosensitized triplet-triplet energy  
211 transfer leads to the overwhelming formation of TT-CPD<sup>59-61</sup>. The biological relevance  
212 of this process was assessed by the observation of dark CPDs in human skin *in vivo*  
213<sup>62</sup>. Their formation was observed even at the highest UVA wavelengths but not in the  
214 visible range<sup>63</sup>. An interesting phenomenon is the fast decrease in the peak of CPDs  
215 following exposure<sup>56, 57, 62</sup>. This could be explained by a faster repair of dark than  
216 immediate CPDs. Formation of dark CPDs requires molecular contact between

217 endoperoxides and bases. It is therefore favoured in open regions of chromatin where  
218 DNA repair is the most efficient. Further work is necessary to confirm this hypothesis  
219 that would help quantifying the biological role of dark CPDs.

## 220 **7.2.3 UVC-induced DNA damage**

### 221 **7.2.3.1 Interest of UVC in photobiology**

222 UVC is absent from the sunlight reaching the surface of Earth and of limited interest in  
223 terms of health effects. However, the recent COVID pandemic has led to a regain of  
224 interest in the UVC-mediated disinfection technologies <sup>64</sup>. This strategy has been used  
225 for many years, with a first germicidal action spectra published as early as 1946 <sup>65</sup> and  
226 confirmed since then by countless works. The maximal efficacy of UVC radiation is  
227 observed at 260-265 nm. In practical applications, equipment use the easily available  
228 254 nm-emitting high-pressure mercury lamp. Its efficacy at this wavelength is  
229 approximately 90% of that at 260 nm. Because 254 nm radiation exhibits severe risks  
230 for skin and eyes <sup>66</sup>, very recent alternatives have been proposed based on higher  
231 energy UVC, mostly at 222 nm. Because they exhibit a lower penetration in tissues,  
232 these photons are expected to be less damaging than 254 nm. It remains though to  
233 determine whether this represents an industrial advantage since all sterilization  
234 devices are protected. One novelty would be to use 222 nm light to directly sterilize  
235 areas of the human body but much deeper investigation on the harmlessness of these  
236 technologies would be necessary. More local application such as surgery site are yet  
237 interesting <sup>67</sup>.

### 238 **7.2.3.2 DNA damage in the UVC range**

239 Exposure to 254 nm radiation exhibits its germicidal properties because it induces large  
240 amounts of damage in the genome of bacteria, yeasts and viruses. This is clearly

241 documented by early works on the formation of pyrimidine dimers in DNA <sup>16, 68</sup>. This  
242 was mostly motivated by the availability of mercury lamps emitting photons with a  
243 wavelength close to the maximal absorption of DNA. Today, UVC is mostly used in  
244 biological studies as a convenient tool for the fast production of significant amounts of  
245 DNA damage. Because it is more efficiently absorbed than UVB, UVC leads to a larger  
246 yield of photodamage. The ratio in UVC-induced yield with respect to UVB is around  
247 10 in bacteria <sup>11</sup>. This trend is different in human skin because UVC is strongly  
248 absorbed by the stratum corneum and the upper layer of the cutaneous tissue. The  
249 yield of CPDs was found to be similar at 260 and 300 nm in the epidermis and almost  
250 1 order of magnitude lower in the dermis <sup>69</sup>. Interestingly, the same decrease in the  
251 action spectrum in the UVC range compared to UVB is observed for skin cancer <sup>70</sup>.  
252 The proportion between the frequencies of the different photoproducts is the same in  
253 the UVC range than with UVB <sup>21</sup>. It should be stressed that this analogy holds only for  
254 low doses of UVC. Indeed, at this wavelength, secondary photoreactions can take  
255 place, in particular for CPDs. The 260 nm absorption of pyrimidine bases is lost upon  
256 formation of the cyclobutane dimer but the resulting CPDs keep an absorption band at  
257 approximately 230 nm with residual absorption at 254 nm. CPDs are thus able to  
258 absorb photons at this wavelength, which triggers a photoreversion reaction into the  
259 original bases <sup>71, 72</sup>. As a result, the dose-dependent formation is not linear but reaches  
260 a plateau <sup>21, 73</sup>. This phenomenon does not take place with UVB that is not absorbed  
261 by CPDs. Because photoreversion of 64-PPs does not occur, the ratio between CPDs  
262 and 64-PPs decreases as the UVC dose increases. An additional issue is that C-  
263 containing CPDs are more susceptible to photoreversion than TT CPD <sup>21, 72</sup>. Therefore,  
264 the ratio between the levels of the four possible CPDs also varies at large UVC dose.  
265 Although most data on UVC-induced photodamage in double stranded B-DNA were

266 obtained at 254 nm, data are available for lower wavelengths for isolated DNA. It was  
267 thus shown that the yields of CPD at 220 and 240 nm represent 80 and 40% of that at  
268 260 nm, respectively <sup>74</sup>. In the 170-200 nm region, where DNA exhibits a second  
269 absorption maximum, the yield of CPD is slightly larger than that determined at 260  
270 nm <sup>74</sup>. In skin, exposure to 222 nm did not lead to formation of CPDs, in contrast to  
271 UVB and, to a lesser extent, to 254 nm radiation <sup>75</sup>. Works carried out on isolated DNA  
272 provided information on the effect of higher energy UVC, typically 195 nm. At this  
273 wavelength, direct ionization of DNA bases is highly efficient and leads to damage of  
274 oxidative origin mostly observed at guanine bases. Their yields is a 6-fold larger yield  
275 than that of CPDs <sup>76, 77</sup>.

### 276 **7.2.3.3 Photochemistry in bacterial spores**

277 Like bacteria, yeasts and other microorganisms, bacterial spores are killed upon UVC  
278 sterilization as the result of massive induction of DNA damage. A major difference is  
279 the nature of the induced photoproducts. In contrast to all other living cells, exposure  
280 of spores to UV radiation does not lead to the formation of CPDs and 64-PPs but to a  
281 dimer involving two adjacent thymine bases, 5-( $\alpha$ -thyminy)-thymine also known as the  
282 spore photoproduct (SP) <sup>78</sup>. This specific photochemistry is explained by the unusual  
283 A-like form of DNA in spores <sup>79-81</sup>. This conformation is induced by the highly  
284 dehydrated core environment and the complexation of large amounts of small acid  
285 soluble proteins to DNA. In addition, the spore is loaded with large concentrations of  
286 dipicolinate that favour the formation of SP <sup>82, 83</sup>. Like CPDs, SP is produced in  
287 maximum yield at the maximal absorption of DNA <sup>84</sup>. However, it is produced at higher  
288 energy (222 nm) in significant yield <sup>85</sup>. Formation of SP is believed to explain the  
289 photoresistance of spores since a very efficient radical-SAM (S-adenosyl-methionine)  
290 repair enzyme is present in the spore and rapidly reverts SP upon germination <sup>86</sup>.



## 291 **7.3 Oxidatively generated DNA damage in cells**

292 Emphasized has been placed in part 2 on the formation of pyrimidine dimers. Sunlight  
293 is also known to induce DNA damage through oxidative pathways. The underlying  
294 mechanisms have been documented by many works on isolated DNA. Formation of  
295 oxidatively generated lesions was also determined *in vitro*.

### 296 **7.3.1 UVB and oxidative stress**

297 Although often discussed for the effect of UVA, oxidatively generated DNA lesions are  
298 also relevant in the effects of UVB. The relative yield of this class of damage with  
299 respect to CPDs is yet very much in favour of the latter. For instance, the difference in  
300 yields of formamidopyrimidine glycosylase (Fpg)- and T4 endonuclease V (T4endoV)-  
301 sensitive sites, corresponding respectively to oxidized guanines and CPDS, is  
302 approximately 1000 in CHO cells in the 290-320 nm range <sup>8</sup>. Similar results were  
303 reported in human fibroblasts <sup>47</sup>. The underlying mechanisms, that may involve  
304 excitation of catalase <sup>87</sup>, cyclooxygenase and reduced nicotinamide adenine  
305 dinucleotide phosphate (NADPH) <sup>88, 89</sup>, remain to be fully elucidated. An interesting  
306 recent result, extensively discussed in the chapter 3 by D. Markovitsi in this volume, is  
307 the possible direct ionization triggered by absorption of UV photons by DNA bases,  
308 even below the energy corresponding to the ionization threshold <sup>90-92</sup>.

### 309 **7.3.2 Main UVA-induced photooxidation pathways**

310 UVA is only poorly absorbed by DNA and does not provide enough energy to induce  
311 photoionization of DNA components. Therefore, all oxidation reactions induced in  
312 UVA-irradiated cells arise from photosensitized reactions. In these processes, UVA  
313 photons are absorbed by endogenous cellular components <sup>93</sup> that, upon excitation,



314 trigger oxidation reactions and release of oxidizing species. Numerous works on model  
315 systems and isolated DNA has provided valuable mechanistic information.

### 316 **7.3.2.1 One-electron oxidation reactions**

317 A first photosensitized process involves electron abstraction from DNA bases and is  
318 known as “type I photosensitization”. This photoreaction has been found to be efficient  
319 with all nucleic bases studied as isolated monomer when the oxidation potential of the  
320 excited photosensitizer is large enough. However, when taking place in double  
321 stranded DNA, one-electron oxidation leads to the sole formation of damage at  
322 guanine bases <sup>94-96</sup>. This is explained by the much lower ionization potential of this  
323 base compared to other DNA components. Consequently, radical cations produced on  
324 T, C or A migrate within DNA to guanine residues where the guanine radical cation  
325 gives rise to oxidation products. Those are mostly 8-oxoGua and 4-hydroxy-5-  
326 formamidopyrimidine (FapyGua). Secondary oxidation products of 8-oxoGua can be  
327 produced at large dose but not under biologically relevant condition.

### 328 **7.2.3.2 Singlet oxygen**

329 Rather than reacting with DNA components, photosensitizers in their excited state may  
330 transfer their energy to dioxygen. Unlike most molecules, the ground state of dioxygen  
331 is a triplet state, which limits its direct reactivity with DNA components. However,  
332 transfer of energy from the triplet excited state of the sensitizers converts it into the  
333 highly reactive singlet oxygen (<sup>1</sup>O<sub>2</sub>) in a “type II photosensitization reaction”. This  
334 species, that is not a radical, readily reacts with double bonds in organic molecules  
335 leading to the formation of endoperoxides and dioxetanes. It can also lead to the  
336 formation of hydroperoxide through the ene-reaction and oxidize sulphur atoms. In

337 DNA, only guanine reacts with  $^1\text{O}_2$  with formation of an endoperoxide that further leads  
338 to the formation of 8-oxoGua as the only reaction product<sup>94, 95, 97</sup>.

### 339 **7.2.3.3 Reactive oxygen species arising from the** 340 **superoxide anion radical**

341 Superoxide anion ( $\text{O}_2^{\bullet-}$ ) is produced in large amounts in UV-irradiated cells as the  
342 result of enzymatic process or by release from mitochondria<sup>98</sup>. Superoxide anion is  
343 poorly reactive with DNA but is at the origin of more damaging species. Upon  
344 dismutation, either catalysed by redox metals or performed by the superoxide  
345 dismutase enzymes,  $\text{O}_2^{\bullet-}$  gives rise to hydrogen peroxide  $\text{H}_2\text{O}_2$ . Hydrogen peroxide is  
346 also unable to directly damage DNA. However, reduced metal ions like  $\text{Fe}^{2+}$  or  $\text{Cu}^+$   
347 may convert it into the highly reactive hydroxyl radical  $\bullet\text{OH}$ . In this reaction, metal ions  
348 are oxidized into  $\text{Fe}^{3+}$  or  $\text{Cu}^{2+}$ . The reducing environment of cells, mostly resulting from  
349 the large concentration in glutathione, allows the conversion of these ions back to their  
350 reduced forms able to react again with  $\text{H}_2\text{O}_2$ . This process is worsened by the release  
351 of iron from its storage proteins upon UVA irradiation<sup>99, 100</sup>. The high reactivity of  $\bullet\text{OH}$   
352 leads to the formation of a wide series of damage to the four DNA bases<sup>99, 100</sup>. Purines  
353 are converted into 8-oxo and formamidopyrimidine derivatives upon attack at the C8  
354 position.  $\bullet\text{OH}$  also reacts efficiently with the C5-C6 double bond of pyrimidines, and  
355 leads to the formation of 5,6-dihydroxy-5,6-dihydro derivatives (thymine and cytosine  
356 glycols) and 5-hydroxycytosine. Oxidation reactions also take place on the methyl  
357 group of thymine with formation of 5-hydroxymethyl- and 5-formyl- uracil.  $\bullet\text{OH}$  can also  
358 perform hydrogen atom abstraction from the deoxyribose moiety of the sugar-  
359 phosphate backbone<sup>99, 100</sup>. Consequently, it is one of the few species that can induce  
360 DNA strand breaks. The superoxide anion not only leads to the formation reactive  
361 oxygen species but also of nitrogen oxidizing derivatives. The most documented

362 pathway involves its reaction with NO that leads to the formation of peroxyxynitrite  
363 HOONO and, after subsequent reaction with CO<sub>2</sub>, of nitrosoperoxy carbonate  
364 ONOOCO<sub>2</sub><sup>-</sup>. While the former compound damages DNA through its decomposition  
365 into •OH<sup>101</sup>, the latter gives rise to carbonate radical anion that is a one-electron  
366 oxidant<sup>102</sup>.

### 367 **7.3.3. Oxidatively generated DNA damage in UVA-** 368 **irradiated cells**

369 Information on the formation of oxidation products in the DNA of UVA irradiated cells  
370 was mostly inferred from enzymatic assays associated with either electrophoretic  
371 analysis or alkaline elution. In these approaches treatment with purified DNA repair  
372 enzymes are added to the protocol in order to convert specific classes of DNA base  
373 damage into strands breaks that add to those directly produced by the irradiation. The  
374 most frequently used enzymes are bacterial Formamidopyrimidine glycosylase and  
375 Endonuclease III that recognize oxidized purines and oxidized pyrimidines,  
376 respectively. T4endoV allows the detection of CPDs. In all reported studies, oxidized  
377 purines, most likely 8-oxoGua, are produced in larger amounts than direct strand  
378 breaks over the entire UVA range<sup>8, 103</sup>. Additional works showed that oxidized  
379 pyrimidines are minor lesions<sup>103</sup>. The distribution of DNA oxidatively generated lesions  
380 in UVA-irradiated cells differs from that induced by the hydroxyl radicals produced by  
381  $\gamma$ -rays and from that induced by singlet oxygen produced by a specific sensitizer. The  
382 ratio between the relative yield of direct strand breaks, Fpg-sensitive sites and Endo-  
383 III sensitive sites were 1/0.47/0.16, 0.37/1/0.4 and 1/0.25/0, respectively<sup>103</sup>. This  
384 observation, combined with the fact that type I photosensitization is believed to be only  
385 weakly involved in the formation of oxidatively generated DNA lesions<sup>97</sup>, led to the  
386 conclusion that 80% of the DNA damaging oxidizing species are singlet oxygen and

387 20% hydroxyl radicals <sup>103</sup>. It should be stressed that the yield of oxidatively generated  
388 lesions is not the same in all cell types. For example, melanocytes are more sensitive  
389 than other cutaneous cells upon UVA irradiation as the result of the presence of  
390 photosensitizing pheomelanin <sup>49, 104-107</sup>.

391 8-OxoGua being the most frequent oxidatively generated lesion, it can be used as a  
392 probe to compare oxidative stress and CPD formation in the UVA range. Using  
393 broadband sources and either enzymatic or chromatographic assays, CPDs have been  
394 detected in larger amounts in all cell types including CHO cells and human  
395 keratinocytes and melanocytes. The ratio between the amounts of CPD and 8-oxoGua  
396 is approximatively 5 <sup>22, 46, 48</sup>, with the exception of melanocytes where the larger yield  
397 of 8-oxoGua leads to a ratio of 1.5 <sup>49</sup>. This ratio is yet wavelength-dependent as shown  
398 in CHO cells where the values are 10 at 340 nm, 5.5 at 365 nm and 1 at 390 nm <sup>8</sup>. It  
399 can thus be concluded from these series of results that oxidatively generated lesions  
400 cannot be considered as the most frequent damaging events of the nuclear DNA in  
401 UVA-irradiated cells. Of course, this does not rule out that oxidative stress exhibits  
402 major effects on other biomolecules and in other cell compartments.

#### 403 **7.4 Spectral composition and photoproduct distribution**

404 Most of the data available on the DNA damaging of sunlight were obtained with pure  
405 UVB or UVA sources. Some more environmentally relevant works used simulated  
406 sunlight that gathered the effects of both spectral ranges. However, only limited  
407 amounts of information are available on the possible combined effects of different  
408 wavelength ranges. The photobiological responses may not be additive and lead to  
409 antagonistic or synergistic effects on the induction of some types of DNA damage.  
410 Occurrence of such phenomena would emphasize the need to take into account the  
411 emission spectra of the UV source. This is partially done when weighted action spectra

412 are used but this approach relies only on additivity. Evidence are already available in  
413 field of DNA damage of such complex spectral effects <sup>108</sup>.

#### 414 **7.4.1 Formation of Dewar valence isomers**

415 Dewar valence isomers <sup>36</sup> are produced when 64-PPs absorb a UV photon and  
416 undergo an intramolecular electrocycloisatation in their pyrimidone ring <sup>37</sup>. The latter  
417 moiety exhibits a maximum absorption at 325 nm in TT and CT 64-PP and at 315 nm  
418 in TC and CC 64-PP <sup>38, 39, 109</sup>. Consequently, UVB is expected to efficiently induce this  
419 reaction. This is actually the case in model systems like small oligonucleotides but  
420 much less in isolated and cellular double-stranded DNA, at least at biologically relevant  
421 doses <sup>12, 21</sup>. This difference is explained by the overwhelming presence of normal  
422 bases that preferentially absorb UVB photons, which are then not available for the  
423 isomerization of 64-PPs <sup>110</sup>. Interestingly, 64-PPs exhibit a residual absorption in the  
424 UVA range. The ratios between the areas under the curve of the absorption spectrum  
425 in the UVB (240-320 nm) and UVA (320-380) are 0.76 for TT 64-PP and 0.44 for TC  
426 64-PP. By comparison, the corresponding value is only 0.02 for DNA. These figures  
427 shows the much lower shielding effect of 64-PP by normal DNA bases in the UVA than  
428 the UVB range. This ability of UVA at photoisomerising 64-PPs was put forward already  
429 in the first article reporting the structure of Dewar in dinucleoside monophosphate <sup>38</sup>.  
430 Since then, several works using different quantification tools have shown that Dewars  
431 are present in significant amounts in cells exposed to simulated sunlight, namely a  
432 combination of UVB and UVA <sup>12, 46, 111, 112</sup>. Additional support for the biological  
433 relevance of Dewar isomer came from the observation of its formation in cells exposed  
434 to natural sunlight <sup>113, 114</sup> and from its unambiguous detection in marine  
435 microorganisms collected in the ocean <sup>115</sup>. Recently, the extent of photoisomerisation  
436 of 64-PPs in isolated DNA exposed to sunlight was reported to depend on the season

437 <sup>116</sup>, following the UVB/UVA ratio. It is difficult to provide a value for the ratio between  
438 the amount of 64-PPs and Dewars generated in DNA by exposure to natural or  
439 simulated sunlight. Indeed, the proportion of Dewars increases at the expense of that  
440 of 64-PPs when the dose increases. All these results could be rationalized in terms of  
441 emission spectrum and absorption at the different wavelengths <sup>110</sup>.

#### 442 **7.4.2. UV-induced formation of sensitizers**

443 Pyrimidine dimers are not the only types of photodamage impacted by the effects of  
444 two UV wavelengths ranges. Although this process has not been directly documented  
445 in cells, test tube experiments strongly suggest that UVB-mediated degradation of  
446 various biomolecules leads to the formation of photosensitizers that increase the extent  
447 of UVA-mediated oxidative stress. A first example are endogenously produced pterin  
448 derivatives <sup>117, 118</sup>. Pterin is a well-known photosensitizer studied for its damaging  
449 properties of biomolecules and its application in photodynamic therapy <sup>119-121</sup>. Another  
450 source of photosensitizing photoproducts is tryptophan. Its main photoproduct is N-  
451 formylkynurenine that is known to exhibit photodynamic properties <sup>122, 123</sup>. UVB  
452 irradiation of tryptophan also generates 6-formylindolo[3,2-b]carbazole (FICZ) which is  
453 also a photosensitizer <sup>124</sup>. The yield of FICZ is yet very low <sup>125</sup> and its role in UVA-  
454 induced oxidative stress is unlikely. Other combinations of wavelengths may enhance  
455 oxidative stress. For example, UVA-induced lipofuscin was reported to photosensitize  
456 keratinocytes to visible light <sup>126</sup>.

#### 457 **7.4.3. Impact of UVA on the repair of UVB-induced dimers**

458 Several works have unambiguously shown that exposure to UVB, especially in a  
459 chronic or repetitive pattern, led to the enhancement of DNA repair capacities <sup>127-131</sup>  
460 and in particular of nucleotide excision repair, which handles pyrimidine dimers.

461 Evidence are also accumulating that UVA exhibits the opposite effects. Exposure to  
462 UVA prior to UVB has been shown to reduce the rate of removal of CPDs, both in  
463 keratinocytes<sup>9</sup> and melanocytes<sup>132</sup>. *In vitro* studies also showed that UVA, alone or in  
464 the presence of photosensitizer, induced oxidative damage to repair proteins<sup>133</sup> like  
465 RPA<sup>134</sup> or PCNA<sup>135</sup>. The combination of these two opposite impacts of UVB and UVA  
466 on DNA repair strongly suggests that the persistence of pyrimidine dimers could  
467 depend on the ratio between these two wavelength ranges in the spectrum of the  
468 incident light.

## 469 **7.5 DNA damage at the nucleotide resolution in cellular DNA**

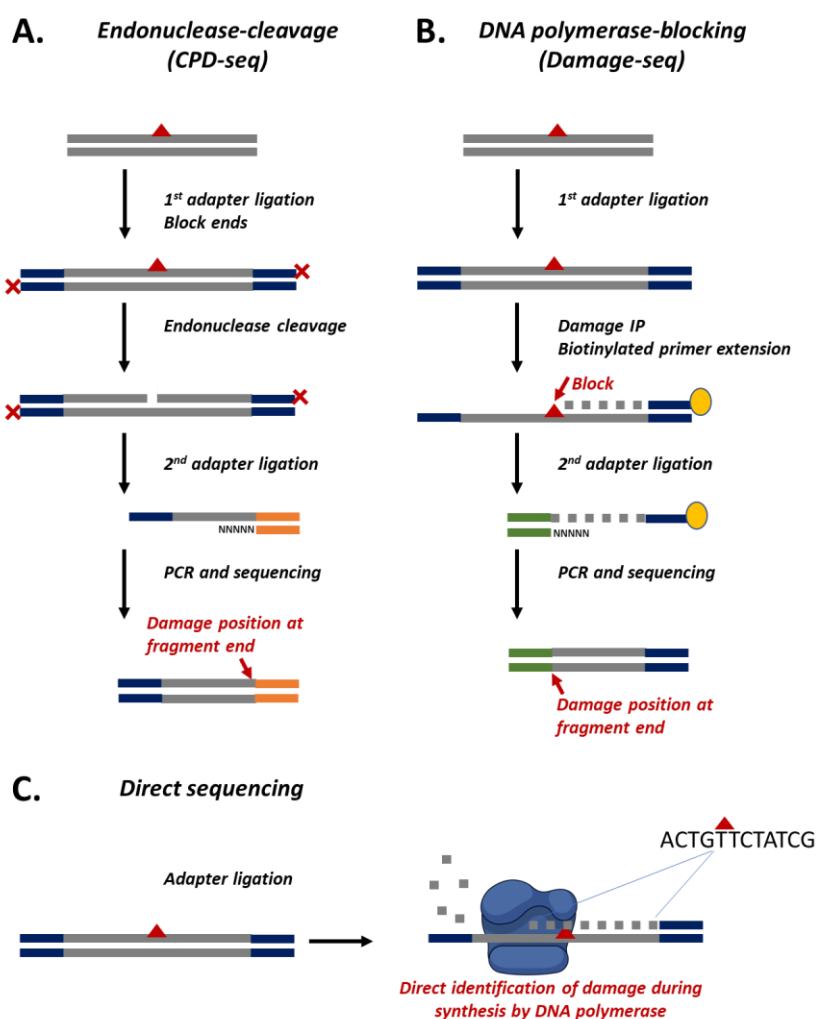
470 The advent of genome sequencing opens new avenues for the analysis of UV-induced  
471 pyrimidine dimers. In recent years, several techniques were developed for the  
472 identification and study of CPDs and 64-PPs at single-nucleotide resolution (Fig. 7.2).  
473 UV dimers have been mapped in bacteria<sup>136</sup>, yeast<sup>29, 137, 138</sup>, and human genomes<sup>6</sup>.  
474<sup>28, 30, 31, 139</sup>. Three major molecular approaches have been applied to pinpoint the  
475 damage positions. The first relies on damage-specific endonucleases to fragment  
476 DNA, and identifies damage sites based on the nucleotides at the fragment ends. CPD-  
477 seq, adduct-seq, and most recently GLOE-seq rely on the T4endoV and were therefore  
478 only applied to CPDs<sup>29-31</sup>. In contrast, excision-seq and UVDE-seq<sup>137, 138</sup> use the UV  
479 damage endonuclease (UVDE) and can map both CPDs and 64-PPs. However, this  
480 technique requires very high damage levels and has not been applied to mammalian  
481 genomes. The second approach, used by HS-Damage-seq<sup>6</sup>, relies on blocking of DNA  
482 polymerases by the pyrimidine dimers. Here, damaged DNA from cells is subjected to  
483 *in vitro* primer extension, and the position of the lesion is identified again based on the  
484 fragment end. Using anti-CPD and anti-64-PP antibodies allows discrimination and  
485 mapping of the two damage types separately. The third and last approach is most



486 straightforward, but is so far limited in its application. This approach relies on  
487 identification of the damage-sites directly during single-molecule real-time (SMRT)  
488 sequencing. Pyrimidine dimers significantly block DNA polymerization and will alter  
489 polymerase kinetics. Direct sequencing of dimers was published in 2011 using  
490 synthetic oligonucleotides<sup>140</sup> and has not significantly advanced since, suggesting a  
491 difficulty of scaling to genomic sequences. The recent RADAR-seq method<sup>136</sup> may  
492 overcome these hurdles since it bypasses the necessity to directly sequence dimers:  
493 it uses T4 endonuclease IV to nick at damage site and *in vitro* synthesis to replace the  
494 dimer with a stretch of modified nucleotides prior to SMRT sequencing. However,  
495 RADAR-seq reduces the resolution of damage detection and has so far only been  
496 applied to *in vitro* irradiated bacterial DNA.

497         Analysis of the specific pyrimidines composing CPDs, performed with different  
498 methods, cell types, and UVC or UVB doses all showed a preference for  
499 TT>TC>CT>CC<sup>6, 28-31</sup>. HS-Damage-seq, excision-seq and UVDE-seq have also been  
500 used to map 64-PP in human and yeast genomes, and have found damages to form  
501 preferentially in TC>TT>CT>CC<sup>6, 137, 138</sup>. These preferences are consistent with the  
502 previous bulk DNA analyses. While UVDE will excise multiple photoproduct types, in  
503 UVDE-seq, UV-irradiated DNA was pre-treated with photolyase to remove CPDs. This  
504 allowed the identification of not only 64-PP but also non-canonical TA and AC  
505 photoproducts<sup>138</sup>. In addition to identifying the specific nucleotides composing the  
506 dimers, sequencing-based methods also provide the immediate sequence context of  
507 dimers. Thus, these methods show enrichment of CPD damage formation within T-  
508 tracks of DNA, and the preference for 64-PP damage formation in TC or TT sequences  
509 flanked by a C upstream and an A downstream of the damaged site<sup>6, 137</sup>.





510  
 511 Figure 7.2. The three major approaches to mapping UV induced dimers. A) Mapping  
 512 UV dimers based on endonuclease cleavage sites. Prior to cleavage free 3'-OH  
 513 groups are blocked in order to obstruct adapter ligation. Shown is the schematic of  
 514 CPD-seq. Adduct-seq, GLOE-seq, excision-seq and UVDE-seq are similar to CPD-  
 515 seq but slightly modified. B) Mapping dimers based on the position at which a DNA  
 516 polymerase is blocked in-vitro (Damage-seq). C) Direct detection of damages  
 517 through SMRT sequencing. Red triangle: UV dimer. Red X: blocked DNA ends.  
 518 Yellow circle: biotin. Figure generated with Biorender.com

519 In the large mammalian genomes, obtaining a quantitative high-resolution map  
 520 of every damageable bipyrimidine site requires extremely high sequencing coverage.  
 521 Most of the studies to date have not produced such high-coverage maps. Instead, in  
 522 order to analyze the chromosomal context of damage formation, studies average  
 523 damage densities over aggregated sequences. These include the study of damage

524 formation over transcription start sites of genes, well-positioned nucleosome dyads or  
525 transcription factor binding sites:

### 526 **7.5.1 Damage formation in genes**

527 In general, the major determinant of CPD damage formation is the frequency of  
528 pyrimidine dimers, primarily TT sequences. This frequency is not uniform in the  
529 genome, and specifically in genes. TT sequences are depleted near the transcription  
530 start sites of genes, and asymmetrically distributed between the transcribed and non-  
531 transcribed strands, resulting in overall lower damage levels on the transcribed strands  
532 of genes <sup>141</sup>.

### 533 **7.5.2 Damage formation in nucleosomal DNA**

534 Nucleosome positions are generally associated with a depletion of TT pairs that could  
535 lead to lower levels of damage <sup>142</sup>. Analysis of CPD formation after normalizing to the  
536 underlying TT frequencies in yeast and human genomes has shown that the rotational  
537 setting of the DNA in the nucleosome affects CPD damage formation: a 10bp  
538 periodicity in CPDs is observed, with peaks in the outward facing rotational settings <sup>29</sup>,  
539 <sup>143</sup>. Control experiments with genomic DNA irradiated *in vitro* did not produce this effect  
540 confirming that this periodicity is indeed a product of nucleosome binding. This  
541 increase in damage frequency at specific rotational settings within a nucleosome can  
542 be explained by the conformational changes in DNA that result in the adjacent  
543 pyrimidine bases assuming a favorable angle for dimer formation. This aspect is  
544 discussed by Gillet et al. in chapter 6 of this book.

### 545 **7.5.3 Damage formation at transcription factor binding sites**

546 Transcription factor binding sites were identified as sites of elevated UV mutagenesis  
547 in melanoma. Several studies assessed damage formation at transcription factor

548 binding sites, focusing on bipyrimidines contained within or adjacent to the consensus  
549 binding motifs. In yeast, Abf1 and Reb1 binding sites were associated with lower CPD  
550 frequencies<sup>29</sup>. In humans, some transcription factors were associated with reduced,  
551 while others with elevated damage frequencies<sup>6, 144</sup>. These altered damage  
552 frequencies were absent in irradiated naked DNA or at unbound motif-sites in cells,  
553 indicating they are a direct result of binding. Like in nucleosomes, binding can alter  
554 DNA conformation and result in favorable or unfavorable angles for dimerization. Three  
555 independent studies identified ETS1 binding sites as hotspots for damage formation,  
556 that were associated with subsequent melanoma mutation hotspots<sup>28, 30, 139</sup>.

557 Higher mutation rates could be a result of higher damage, but could also be the product  
558 of lower repair efficiency. Indeed, a recent study suggests that it is primarily the lower  
559 repair efficiency at transcription factor-bound sites that promotes mutagenesis<sup>144</sup>.  
560 Repair of UV damages is extensively discussed by John J. Wyrick in chapter 12 of this  
561 volume. A key factor in untangling the relative contributions of damage formation  
562 versus repair will be to understand how damages affect protein binding in chromatin,  
563 including nucleosomes and transcription factors, a subject far less studied to date.

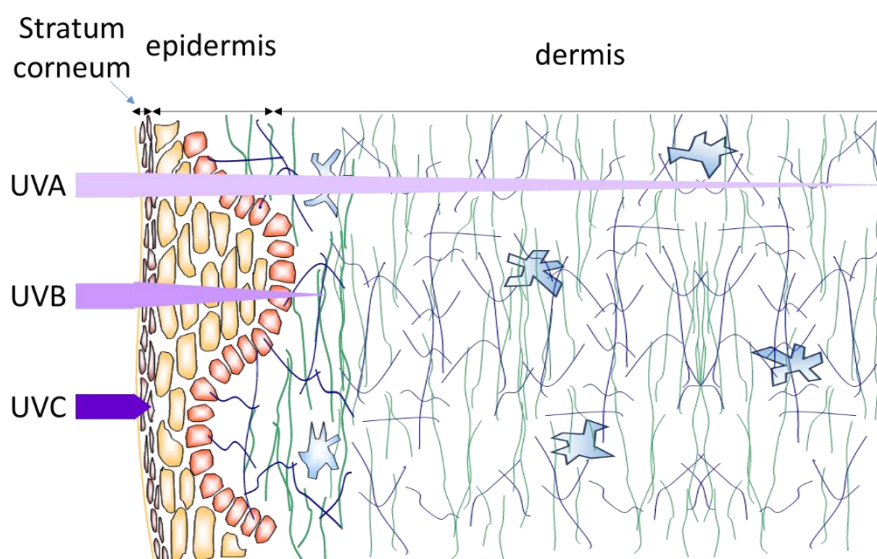
## 564 **7.6 UV-induced DNA damage in skin**

565 Most of the information discussed above were obtained in *in vitro* models. The amount  
566 of information in skin is less abundant, mostly because of limitation in sample size and  
567 technical issues. However, data obtained by immunological assays and in particular  
568 immunohistochemistry, and chromatographic techniques provided insight on the  
569 impact of the organization of the cutaneous tissues on the formation of photodamage.  
570 The vast majority of the information available concerns pyrimidine dimers. Their results  
571 show that the skin morphology drastically affects the level of DNA damage (Fig. 7.3).

572 It should also be stressed that eyes represent another target of solar UV. The formation  
573 and repair of CPDs have only been investigated recently <sup>145-148</sup>.

#### 574 **7.6.1 Yield of lesions in skin**

575 UVB and UVA induce the formation of CPDs in both keratinocytes and melanocytes in  
576 the same yield in skin <sup>50</sup>. Interestingly, the mean value of the yield of CPDs induced by  
577 UVB in DNA of the epidermis is lower than in culture of keratinocytes, which are the  
578 most frequent cell types in this skin compartment <sup>22</sup>. This can be first explained by the  
579 protective effect of the stratum corneum. An additional explanation is the shielding  
580 effect of the different layers of keratinocytes in the epidermis <sup>112</sup>. This effect is  
581 wavelength-dependent with a decrease in the CPDs yield per cell layer 15 faster at  
582 260 nm than at 230. Determination of accurate quantitative data also showed that the  
583 yield of CPDs was roughly 2 and 4 orders of magnitude lower at 320 and 365 nm,  
584 respectively, compared to 290 nm in both dermis and epidermis <sup>69</sup>. In the same study,  
585 64-PPs were found to be produced in a constant ratio from 260 to 310 nm, and then  
586 strongly decrease at higher wavelengths. In contrast to UVB, UVA is poorly absorbed  
587 by the stratum corneum and penetrates through the keratinocytes layers without  
588 significant attenuation. These observations explain why the ratio between the yield of  
589 CPD in the UVB and UVA ranges is lower in skin than in cultured cells <sup>22, 24, 48</sup>. It should  
590 be stressed that immunohistochemistry results showed that the level of UVA-induced  
591 CPDs was slightly higher in the basal layer than in layers located above. <sup>149</sup>. This  
592 suggested the occurrence of a reflexion of UVA takes place at the dermal-epidermal  
593 junction.



594  
 595 *Figure 7.3: Penetration of UV radiation in human skin. The highly energetic UVC*  
 596 *radiation are rapidly absorbed by the stratum corneum. UVB is absorbed in the*  
 597 *epidermis and reaches the top of the dermis. In contrast, UVA is weakly attenuated*  
 598 *and interacts with the whole dermis. In terms cell types, keratinocytes present in*  
 599 *dense layers in the epidermis are much more affected by both UVA and UVB than*  
 600 *fibroblasts sparsely spread in the dermal extracellular matrix.*

601

### 602 **7.6.2 Effect of phototype on the formation of CPDs**

603 Phototypes is a convenient way to stratify the different skin types, which mostly reflect  
 604 ethnic origins. In Caucasian, the risk of burning and the ability to tan upon exposure to  
 605 sunlight has led to the definition of phototypes I (fair skin) to IV (brown skin).  
 606 Phototypes V and VI are Asian and dark brown skins, respectively. A high skin  
 607 phototype is known to be highly protective against skin cancer, as exemplified by  
 608 studies carried out in areas harbouring fair- and dark-skinned populations<sup>150-152</sup>. On  
 609 the average, protection factors of 20 and 70 against melanoma and carcinomas,  
 610 respectively, were observed when skin of phototypes VI were compared to phototype  
 611 II<sup>153, 154</sup>. This was only partially explained by the decrease in the mean level of CPD in  
 612 keratinocytes that was found to be only 10-times lower in skin of phototype VI

613 compared to II following exposure to simulated sunlight or UVB<sup>62, 155</sup>. The same values  
614 were observed for both immediate and dark CPDs<sup>62</sup>. The latter result further suggests  
615 that photooxidation of melanin is not the only mechanism at the origin of dark CPDs.  
616 A better understanding of the impact of the phototype and of the melanin content was  
617 provided by experiments assessing the distribution of melanin and of the yield of CPDs.  
618 These works unambiguously showed that the best protection against CPDs between  
619 dark and fair skins was observed in basal layer, where the largest proportion of melanin  
620 is stored in dark skin<sup>155-157</sup>. The basal layer, that harbours the cells at the origin of  
621 melanomas and basal cell carcinomas, is much more protected than the rest of the  
622 epidermis. It should be stressed that these strong protective effects are no longer  
623 observed when less extreme phototypes are concerned. The ratio between the yield  
624 of CPDs in phototype II and IV is only approximately 1.5<sup>24, 158-160</sup>. Another interesting  
625 data regarding pigmentation is that tanning of Caucasian skin affords only a weak  
626 protection of a factor 2 against the formation of CPDs<sup>160-162</sup>.

## 627 **7.7 Mutagenic consequences of DNA photodamage**

628 The biological consequences of DNA photodamage in terms of carcinogenesis are  
629 mostly driven by their ability to induce mutations. A first requisite for a lesion to be  
630 mutagenic is that it escapes DNA repair as observed for pyrimidine dimers. The  
631 mutagenicity of a photodamage also depends on its chemical structure and the  
632 resulting impact on the coding properties upon replication of DNA. The combination of  
633 all the features explain the mutation spectra observed in tumours

### 634 **7.7.1. *In vitro* data of UV-induced mutagenesis**

635 UV-mutagenesis is investigated for years. The first works involved irradiation of  
636 plasmids further introduced and replicated in bacteria. These early studies showed that

637 UVB and UVC mostly led to mutation at bipyrimidine sites. The subsequent works took  
638 advantage of progress in oligonucleotide synthesis to study the specific mutational  
639 properties of individual pyrimidine dimers with purified polymerases or following  
640 incorporation in plasmids and replication in cells <sup>163-167</sup>. It was thus observed that TT  
641 CPD was poorly mutagenic in contrast to TT 64-PP mostly because of differences in  
642 impact of the lesions on the local structure of DNA. In contrast to TT CPD, deaminated  
643 TC CPD (TU CPD) were highly mutagenic, leading to C→T transitions because U  
644 codes like T during replication. The TC 64-PP was less mutagenic than the  
645 corresponding TT photoproduct <sup>168</sup>. In contrast, the TT Dewar was more mutagenic  
646 than the TC Dewar and less than the TT 64-PP. It is worth mentioning that in  
647 mammalian cells, in addition to deamination <sup>41, 169</sup> and structural modifications,  
648 mutagenesis of UV-induced photoproducts is largely explained by the role of  
649 translesional polymerases <sup>170-172</sup>, as discussed in the chapter 16 by Menck et al. in this  
650 book. Some of these enzymes, like polymerase  $\eta$ , are referred to as “error-free” when  
651 bypassing pyrimidine dimers. They are thus expected to accurately incorporate A  
652 opposite T in TT CPDs, but also opposite U that would arise from C deamination in TC  
653 dimers. It should be stressed that experiments involving cells <sup>20</sup> or mice <sup>173</sup> transfected  
654 with specific repair enzymes led to the conclusion that these mutations mostly result  
655 from CPDs rather than 64-PPs, which are very efficiently repaired. Another important  
656 feature is that C→T transitions at TC sites are also predominant in cells exposed to  
657 UVA <sup>45, 174, 175</sup> in line with the predominant formation of CPDs in this wavelength range.  
658 The bulk of these data helped defining a UV mutational signature where C→T transition  
659 at TC sites and CC→TT tandem mutations were predominant <sup>176, 177</sup>.

660 *In vitro* mutational data are also available for oxidatively generated damage.  
661 8-OxoGua, following misincorporation of adenine upon replication leads to G→T



662 transversion <sup>178</sup>. Information were also obtained on the Fapy derivatives that show that  
663 FapyGua leads to G→T transversion while 4,6-Diamino-5-formamidopyrimidine  
664 (FapyAde) is poorly mutagenic <sup>179</sup>. Among thymine oxidation products, thymine glycols  
665 are strongly blocking lesions but poorly mutagenic. 5-Formyluracil also leads to a low  
666 mutation frequency <sup>180</sup>. In contrast, cytosine oxidation products are mutagenic, mostly  
667 following deamination <sup>181, 182</sup>. The contribution of these mutations to UVA-mutational  
668 signature is yet limited. The G→T transversion typical of the most frequent oxidatively  
669 generated lesions is a minor mutation, with the exception of one work involving  
670 mutation analyses in tumours collected in the basal layer <sup>183</sup>. Whole genome  
671 sequencing analysis of the mutation induced by UVA in xeroderma pigmentosum  
672 variant human cells failed to detect a significant contribution of oxidative damage but  
673 rather the mutation signature of pyrimidine dimers <sup>184</sup> with frequent mutations at  
674 bipyrimidine sites. Mutation at adenine is also observed <sup>185</sup> while adenine oxidation  
675 products are not frequent upon UVA irradiation.

### 676 **7.7.2. Next generation sequencing of human tumours**

677 Sequencing of specific genes in human tumours such as p53 has confirmed the  
678 presence of the UV signature <sup>186-188</sup>. The development of modern and fast sequencing  
679 techniques, which revolutionized the field of genomics, provided a novel and  
680 outstanding perspective on the mutations underlying human cancers. Next generation  
681 sequencing techniques have been used to determine millions of mutations present in  
682 thousands of tumours collected from different types of cancers <sup>189, 190</sup>. In the field of  
683 skin carcinogenesis, a first interesting result is that, together with lung cancers,  
684 melanoma is one of the cancer type accumulating the largest number of mutations per  
685 tumour <sup>190-192</sup>. The value is more than one order of magnitude larger than, for example,  
686 in leukaemia or medulloblastoma. This can be explained by the fact that skin is



687 constantly exposed to sunlight and accumulates numerous DNA damage and their  
 688 resulting mutations during the development of the tumour. An interesting output of this  
 689 sequencing effort is the statistical analysis of the databank that made possible the  
 690 determination of mutational signatures <sup>193, 194</sup> available on-line from the COSMIC  
 691 consortium <sup>195</sup>. Signatures bearing mutations at bipyrimidine sites (Table 7.2) are  
 692 observed with a high frequency in melanoma <sup>190, 196-199</sup>, basal cell carcinoma <sup>200, 201</sup>,  
 693 squamous cell carcinoma <sup>202</sup> and cutaneous T cell lymphoma <sup>203</sup>. They are basically  
 694 absent from other cancer types. In the field of melanoma, the same approach allowed  
 695 to show that acral and mucosal melanomas do not exhibit the same signature <sup>197, 204</sup>.  
 696 Another interesting information provided by these techniques is related to a mutational  
 697 signature associated with oxidative stress and 8-oxoGua. In the COSMIC database,  
 698 this signature is observed in one third of the breast, prostate and stomach cancers but  
 699 not in skin cancer. A last comment regarding melanoma is the high frequency of a A→T  
 700 transversion leading to the *BRAF*<sup>V600E</sup> mutation <sup>205</sup>. This mutation does not take place  
 701 at a bipyrimidine site and does not correspond to known oxidative lesions. In addition,  
 702 it is also frequent in a number of internal cancers and may thus not be of  
 703 photobiological origin. However, recent UVDE-seq results in UVC-irradiated yeast  
 704 proposed a role for AT dimers <sup>138</sup>, although these photoproducts have been observed  
 705 only in test tube experiments and in much lower yield than CPDs <sup>206, 207</sup>.

706 *Table 7.2: Proportion (in %) of different mutation signatures determined in the*  
 707 *COSMIC\* database for skin cancers. Results represents the ratio between the*  
 708 *number of tumours exhibiting each signature and the number total number of tumour*  
 709 *of each cancer. BCC: basal cell carcinoma, SCC: squamous cell carcinoma.*

signature	7a	7b	7c	7d	tandem1	18
Mutations	C to T at TC	C-to T at TC and CC	T to A and T to C	T to C and C to T	CC to TT	oxydation
Melanoma	84	82	40	55	100	n.d.**
BCC	100	59	23	41	-	n.d.**

SCC	98	100	74	90	-	n.d.**
-----	----	-----	----	----	---	--------

710 \*: 195

711 \*\*: not detected

712

### 713 Abbreviations :

714 64-PP: Pyrimidine (6-4) pyrimidone photoproduct; 8-oxoGua: 8-oxo-7,8-  
 715 dihydroguanine; BCC: basal cell carcinoma; CHO: Chinese hamster ovary cells; CPD:  
 716 cyclobutane pyrimidine dimers; Dewar: Dewar valence isomer of 64-PP; FapyAde: 4,6-  
 717 Diamino-5-formamidopyrimidine; FapyGua: 4-hydroxy-5-formamidopyrimidine; FICZ :  
 718 6-Formylindolo[3,2-b]carbazole; Fpg: formamidopyrimidine glycosylase; SAM S-  
 719 adenosyl-methionine; SCC: squamous cell carcinoma; SMRT: single-molecule real-  
 720 time sequencing; SP: spore photoproduct (5-(a-thyminy)-thymine); T4endoV:  
 721 endonuclease V of phage T4; UVDE: UV damage endonuclease

722

### 723 References

- 724 1. N. Kobayashi, S. Katsumi, K. Imoto, A. Nakagawa, S. Miyagawa, M. Furumura and T. Mori,  
 725 *Pigment Cell Res.*, 2001, **14**, 94-102.  
 726 2. D. Mitchell and B. Brooks, *Photochem. Photobiol.*, 2010, **86**, 2-17.  
 727 3. G. P. Pfeifer, R. Drouin and G. P. Holmquist, *Mutat. Res.*, 1993, **288**, 39-46.  
 728 4. T. Douki, *Photochem. Photobiol. Sci.*, 2013, **12**, 1286-1302.  
 729 5. S. Adar, J. Hu, J. D. Lieb and A. Sancar, *Proc. Natl. Acad. Sci. USA*, 2016, **113**, E2124-2133.  
 730 6. J. Hu, O. Adebali, S. Adar and A. Sancar, *Proc. Natl. Acad. Sci. USA*, 2017, **114**, 6758-6763.  
 731 7. A. R. Collins, V. L. Dobson, M. Dusinska, G. Kennedy and R. Stetina, *Mutat. Res.*, 1997, **375**,  
 732 183-193.  
 733 8. C. Kielbassa, L. Roza and B. Epe, *Carcinogenesis*, 1997, **18**, 811-816.  
 734 9. S. Courdavault, C. Baudouin, M. Charveron, B. Canghilem, A. Favier, J. Cadet and T. Douki,  
 735 *DNA Repair*, 2005, **4**, 836-844.  
 736 10. S. Courdavault, C. Baudouin, S. Sauvaigo, S. Mouret, S. Candéias, M. Charveron, A. Favier, J.  
 737 Cadet and T. Douki, *Photochem. Photobiol.*, 2004, **79**, 145-151.  
 738 11. D. L. Mitchell, J. Jen and J. E. Cleaver, *Photochem. Photobiol.*, 1991, **54**, 741-746.  
 739 12. D. Perdiz, P. Grof, M. Mezzina, O. Nikaido, E. Moustacchi and E. Sage, *J. Biol. Chem.*, 2000,  
 740 **275**, 26732-26742.  
 741 13. B. S. Rosenstein and D. L. Mitchell, *Photochem. Photobiol.*, 1987, **45**, 775-780.  
 742 14. J. E. Frederick, H. E. Snell and E. K. Haywood, *Photochem. Photobiol.*, 1989, **50**, 443-450.  
 743 15. C. Marionnet, C. Tricaud and F. Bernerd, *Int. J. Molec. Sci.*, 2015, **16**, 68-90.  
 744 16. A. J. Varghese, in *Photophysiology*, Academic Press, New-York, 1972, vol. 7, pp. 207-274.  
 745 17. S. Tommasi, M. F. Denissenko and G. P. Pfeifer, *Cancer Res.*, 1997, **57**, 4727-4730.  
 746 18. R. Drouin and J. P. Therrien, *Photochem. Photobiol.*, 1997, **66**, 719-726.  
 747 19. J.-H. Yoon, C.-S. Lee, T. R. O'Connor, A. Yasui and G. P. Pfeifer, *J. Mol. Biol.*, 2000, **299**, 681-  
 748 693.  
 749 20. Y. H. You, D. H. Lee, J. H. Yoon, S. Nakajima, A. Yasui and G. P. Pfeifer, *J. Biol. Chem.*, 2001,  
 750 **276**, 44688-44694.  
 751 21. T. Douki and J. Cadet, *Biochemistry*, 2001, **40**, 2495-2501.

- 752 22. S. Mouret, C. Baudouin, M. Charveron, A. Favier, J. Cadet and T. Douki, *Proc. Natl. Acad. Sci. USA*, 2006, **103**, 13765-13770.
- 753
- 754 23. P. J. Rochette, S. Lacoste, J. P. Therrien, N. Bastien, D. E. Brash and R. Drouin, *Mutat. Res.*, 2009, **665**, 7-13.
- 755
- 756 24. S. Mouret, M. T. Leccia, J. L. Bourrain, T. Douki and J. C. Beani, *J. Invest. Dermatol.*, 2011, **131**, 1539-1546.
- 757
- 758 25. N. Bastien, J. P. Therrien and R. Drouin, *Photochem. Photobiol. Sci.*, 2013, **12**, 1544-1554.
- 759 26. D. L. Mitchell, J. P. Allison and R. S. Nairn, *Radiat. Res.*, 1990, **123**, 299-303.
- 760 27. S. Mouret, M. Charveron, A. Favier, J. Cadet and T. Douki, *DNA Repair*, 2008, **7**, 704-712.
- 761 28. K. Elliott, M. Bostrom, S. Filges, M. Lindberg, J. Van den Eynden, A. Stahlberg, A. R. Clausen and E. Larsson, *Plos Genetics*, 2018, **14**.
- 762
- 763 29. P. Mao, M. J. Smerdon, S. A. Roberts and J. J. Wyrick, *Proc. Natl. Acad. Sci. USA*, 2016, **113**, 9057-9062.
- 764
- 765 30. S. Premi, L. Han, S. Mehta, J. Knight, D. J. Zhao, M. A. Palmatier, K. Kornacker and D. E. Brash, *Proc. Natl. Acad. Sci. USA*, 2019, **116**, 24196-24205.
- 766
- 767 31. A. M. Sriramachandran, G. Petrosino, M. Mendez-Lago, A. J. Schafer, L. S. Batista-Nascimento, N. Zilio and H. D. Ulrich, *Mol. Cell*, 2020, **78**, 975-+.
- 768
- 769 32. S. Matallana-Surget, J. A. Meador, F. Joux and T. Douki, *Photochem. Photobiol. Sci.*, 2008, **7**, 794-801.
- 770
- 771 33. L. Martinez-Fernandez, A. Banyasz, L. Esposito, D. Markovitsi and R. Improta, *Signal Transduct Target Ther*, 2017, **2**, 17021.
- 772
- 773 34. Y.-H. You and G. P. Pfeifer, *J. Mol. Biol.*, 1999, **293**, 493-503.
- 774 35. A. Banyasz, L. Esposito, T. Douki, M. Perron, C. Lepori, R. Improta and D. Markovitsi, *J. Phys. Chem. B*, 2016, **120**, 4232-4242.
- 775
- 776 36. T. Douki and E. Sage, *Photochem. Photobiol. Sci.*, 2015, **15**, 24-30.
- 777 37. K. Haiser, B. P. Fingerhut, K. Heil, A. Glas, T. T. Herzog, B. M. Pilles, W. J. Schreier, W. Zinth, R. de Vivie-Riedle and T. Carell, *Angew. Chem. Int. Ed.*, 2012, **51**, 408-411.
- 778
- 779 38. J.-S. Taylor and M. P. Cohrs, *J. Am. Chem. Soc.*, 1987, **109**, 2834-2835.
- 780 39. J.-S. Taylor, H.-L. Lu and J. J. Kotyk, *Photochem. Photobiol.*, 1990, **51**, 161-167.
- 781 40. Y. Barak, O. Cohen-fix and Z. Livneh, *J. Biol. Chem.*, 1995, **270**, 24174-24179.
- 782 41. L. A. Frederico, T. A. Kunkel and B. Ramsay Shaw, *Biochemistry*, 1990, **29**, 2532-2537.
- 783 42. I. Tessman, M. A. Kennedy and S. K. Liu, *J. Mol. Biol.*, 1994, **235**, 807-812.
- 784 43. J. C. Sutherland and K. P. Griffin, *Radiat. Res.*, 1981, **86**, 399-409.
- 785 44. R. M. Tyrrell, *Photochem. Photobiol.*, 1973, **17**, 69-73.
- 786 45. P. J. Rochette, J.-P. Therrien, R. Drouin, D. Perdiz, N. Bastien, E. A. Drobetsky and E. Sage, *Nucleic Acids Res.*, 2003, **31**, 2786-2794.
- 787
- 788 46. T. Douki, A. Reynaud-Angelin, J. Cadet and E. Sage, *Biochemistry*, 2003, **42**, 9221-9226.
- 789 47. E. Kvam and R. M. Tyrrell, *Carcinogenesis*, 1997, **18**, 2379-2384.
- 790 48. S. Courdavault, C. Baudouin, M. Charveron, A. Favier, J. Cadet and T. Douki, *Mutat. Res.*, 2004, **556**, 135-142.
- 791
- 792 49. S. Mouret, A. Forestier and T. Douki, *Photochem. Photobiol. Sci.*, 2012, **11**, 155-162.
- 793 50. A. R. Young, C. S. Potten, O. Nikaido, P. G. Parsons, J. Boenders, J. M. Ramsden and C. A. Chadmick, *J. Invest. Dermatol.*, 1998, **111**, 936-940.
- 794
- 795 51. F. E. Quaitte, B. M. Sutherland and J. C. Sutherland, *Nature*, 1992, **358**, 576-578.
- 796 52. Z. Kuluncsics, D. Perdiz, E. Brulay, B. Muel and E. Sage, *J. Photochem. Photobiol. B: Biol.*, 1999, **49**, 71-80.
- 797
- 798 53. S. Mouret, C. Philippe, J. Gracia-Chantegrel, A. Banyasz, S. Karpati, D. Markovitsi and T. Douki *Org. Biomolec. Chem.*, 2010, **8**, 1706-1711.
- 799
- 800 54. Y. Jiang, M. Rabbi, M. Kim, C. H. Ke, W. Lee, R. L. Clark, P. A. Mieczkowski and P. E. Marszalek, *Biophys. J.*, 2009, **96**, 1151-1158.
- 801
- 802 55. A. Banyasz, T. Douki, R. Improta, T. Gustavsson, D. Onidas, I. Vaya, M. Perron and D. Markovitsi, *J. Am. Chem. Soc.*, 2012, **134**, 14834-14845.
- 803
- 804 56. S. Premi, S. Wallisch, C. M. Mano, A. B. Weiner, A. Bacchiocchi, K. Wakamatsu, E. J. Bechara, R. Halaban, T. Douki and D. E. Brash, *Science*, 2016, **347**, 842-847.
- 805
- 806 57. G. J. Delinasios, M. Karbaschi, M. S. Cooke and A. R. Young, *Sci. Rep.*, 2018, **8**.
- 807 58. W. Adam, C. R. Sahamoller and A. Schonberger, *J. Am. Chem. Soc.*, 1997, **119**, 719-723.
- 808 59. T. Douki, I. Berard, A. Wack and S. Andra, *Chem. Eur. J.*, 2014, **20**, 5787-5794.
- 809 60. A. A. Lamola, *Pure Appl. Chem.*, 1970, **24**, 599-610.
- 810 61. M. H. Patrick and J. M. Snow, *Photochem. Photobiol.*, 1977, **25**, 373-384.

- 811 62. D. Fajuyigbe, T. Douki, A. van Dijk, R. P. E. Sarkany and A. R. Young, *Pigment Cell Melanoma Res.*, 2020.
- 812
- 813 63. K. P. Lawrence, T. Douki, R. P. E. Sarkany, S. Acker, B. Herzog and A. R. Young, *Sci. Rep.*, 2018, **8**, 12722.
- 814
- 815 64. Y. Kebbi, A. I. Muhammad, A. S. Sant'Ana, L. do Prado-Silva, D. H. Liu and T. Ding, *Compr Rev Food Sci F*, 2020, **19**, 3501-3527.
- 816
- 817 65. M. Luckiesh and A. H. Taylor, *J Opt Soc Am*, 1946, **36**, 227-234.
- 818 66. E. a. E. R. SCHEER (Scientific Committee on Health, *Opinion on biological effects of UV-C radiation relevant to health with particular reference to UV-C lamps*, European Commission, 2017.
- 819
- 820
- 821 67. T. Fukui, T. Niikura, T. Oda, Y. Kumabe, H. Ohashi, M. Sasaki, T. Igarashi, M. Kunisada, N. Yamano, K. Oel, T. Matsumoto, T. Matsushita, S. Hayashi, C. Nishigori and R. Kuroda, *Plos One*, 2020, **15**.
- 822
- 823
- 824 68. S. Y. Wang, in *Photochemistry and Photobiology of Nucleic Acids*, Academic Press, New-York, 1976, vol. 1, pp. 295-356.
- 825
- 826 69. H. Ikehata, T. Mori, Y. Kamei, T. Douki, J. Cadet and M. Yamamoto, *Photochem. Photobiol.*, 2020, **96**, 94-104.
- 827
- 828 70. F. R. de Gruijl, *Eur. J. Cancer*, 1999, **35**, 2003-2009.
- 829 71. H. E. Johns, S. A. Rapaport and M. Delbück, *J. Mol. Biol.*, 1962, **4**, 104-114.
- 830 72. D. G. E. Lemaire and B. P. Ruzsicska, *Photochem. Photobiol.*, 1993, **57**, 755-769.
- 831 73. T. Douki, M. Court, S. Sauvaigo, F. Odin and J. Cadet, *J. Biol. Chem.*, 2000, **275**, 11678-11685.
- 832 74. T. Matsunaga, K. Hieda and O. Nikaido, *Photochem Photobiol*, 1991, **54**, 403-410.
- 833 75. N. Yamano, M. Kunisada, S. Kaidzu, K. Sugihara, A. Nishiaki-Sawada, H. Ohashi, A. Yoshioka, T. Igarashi, A. Ohira, M. Tanito and C. Nishigori, *Photochem. Photobiol.*, 2020, **96**, 853-862.
- 834 76. T. Melvin, S. Cunniffe, D. Papworth, T. Roldanarjona and P. O'Neill, *Photochem. Photobiol.*, 1997, **65**, 660-665.
- 835 77. T. Melvin, S. M. T. Cunniffe, P. O'Neill, A. W. Parker and T. RoldanArjona, *Nucleic Acids Res.*, 1998, **26**, 4935-4942.
- 836
- 837
- 838
- 839 78. J. E. Donnellan and R. B. Setlow, *Science*, 1965, **149**, 308-310.
- 840 79. W. L. Nicholson, B. Setlow and P. Setlow, *Proc. Natl. Acad. Sci. USA*, 1991, **88**, 8288-8292.
- 841 80. W. L. Nicholson, B. Setlow and P. Setlow, *Astrobiology*, 2002, **2**, 417-425.
- 842 81. A. Frances-Monerris, C. Hognon, T. Douki and A. Monari, *Chem. Eur. J.*, 2020, **26**, 14236-14241.
- 843
- 844 82. T. Douki, B. Setlow and P. Setlow, *Photochem. Photobiol. Sci.*, 2005, **4**, 951-957.
- 845 83. B. Setlow and P. Setlow, *Appl. Environ. Microbiol.*, 1993, **59**, 640-643.
- 846 84. C. Lindberg and G. Horneck, *J. Photochem. Photobiol. B-Biol.*, 1991, **11**, 69-80.
- 847 85. W. Taylor, E. Camilleri, D. L. Craft, G. Korza, M. Rocha Granados, J. Peterson, R. Szczpaniak, S. K. Weller, R. Moeller, T. Douki, W. W. K. Mok and P. Setlow, *Appl Environ Microbiol*, 2020, **86**, e03039-03019.
- 848
- 849
- 850 86. O. Berteau and A. Benjdia, *Photochem. Photobiol.*, 2017, **93**, 67-77.
- 851 87. M. Horikawa-Miura, N. Matsuda, M. Yoshida, Y. Okumura, T. Mori and M. Watanabe, *Radiat. Res.*, 2007, **167**, 655-662.
- 852
- 853 88. S. M. Beak, Y. S. Lee and J. A. Kim, *Biochimie*, 2004, **86**, 425-429.
- 854 89. H. Wang and I. E. Kochevar, *Free Radic. Biol. Med.*, 2005, **38**, 890-897.
- 855 90. A. Banyasz, T. Kelola, L. Martinez-Fernandez, R. Improta and D. Markovitsi, *Faraday Discussions*, 2018, **207**, 181-197.
- 856
- 857 91. A. Banyasz, L. Martinez-Fernandez, C. Balty, M. Perron, T. Douki, R. Improta and D. Markovitsi, *J. Am. Chem. Soc.*, 2017, **139**, 10561-10568.
- 858
- 859 92. M. Gomez-Mendoza, A. Banyasz, T. Douki, D. Markovitsi and J. L. Ravanat, *J. Phys. Chem. Lett.*, 2016, **7**, 3945-3948.
- 860
- 861 93. G. T. Wondrak, M. K. Jacobson and E. L. Jacobson, *Photochem. Photobiol. Sci.*, 2006, **5**, 215-237.
- 862
- 863 94. J. Cadet and T. Douki, *Photochem. Photobiol. Sci.*, 2018, **17**, 1816-1841.
- 864 95. J. Cadet, A. Grand and T. Douki, in *Photoinduced Phenomena in Nucleic Acids II: DNA Fragments and Phenomenological Aspects*, eds. M. Barbatti, A. C. Borin and S. Ullrich, Springer-Verlag Berlin, Berlin, 2015, vol. 356, pp. 249-275.
- 865
- 866
- 867 96. J. Cadet, T. Douki and J. L. Ravanat, *Accounts Chem. Res.*, 2008, **41**, 1075-1083.
- 868 97. P. Di Mascio, G. R. Martinez, S. Miyamoto, G. E. Ronsein, M. H. G. Medeiros and J. Cadet, *Chem. Rev.*, 2019, **119**, 2043-2086.
- 869



- 870 98. R. Gniadecki, T. Thorn, J. Vicanova, A. B. Petersen and H. C. Wulf, *J. Cell. Biochem.*, 2000,  
871 **80**, 216-222.
- 872 99. A. Aroun, J. L. Zhong, R. M. Tyrrell and C. Pourzand, *Photochem. Photobiol. Sci.*, 2012, **11**,  
873 118-134.
- 874 100. C. Pourzand, R. D. Watkin, J. E. Brown and R. M. Tyrrell, *Proc. Natl. Acad. Sci. USA*, 1999, **96**,  
875 6751-6756.
- 876 101. L. J. Kennedy, K. Moore, J. L. Caulfield, S. R. Tannenbaum and P. C. Dedon, *Chem. Res.*  
877 *Toxicol.*, 1997, **10**, 386-392.
- 878 102. Y. A. Lee, B. H. Yun, S. K. Kim, Y. Margolin, P. C. Dedon, N. E. Geacintov and V. Shafirovich,  
879 *Chemistry*, 2007, **13**, 4571-4581.
- 880 103. J.-P. Pouget, T. Douki, M.-J. Richard and J. Cadet, *Chem. Res. Toxicol.*, 2000, **13**, 541-549.
- 881 104. E. Kvam and R. M. Tyrrell, *J. Invest. Dermatol.*, 1999, **113**, 209-213.
- 882 105. H. T. Wang, B. Choi and M. S. Tang, *Proc. Natl. Acad. Sci. USA*, 2010, **107**, 12180-12185.
- 883 106. E. Wenczl, G. P. van der Schans, L. Roza, R. Kolb, N. Smit and A. A. Schothorst, *J. Invest.*  
884 *Dermatol.*, 1998, **110**, 693-693.
- 885 107. E. Wenczl, G. P. Van der Schans, L. Roza, R. M. Kolb, A. J. Timmerman, N. P. Smit, S. Pavel  
886 and A. A. Schothorst, *J. Invest. Dermatol.*, 1998, **111**, 678-682.
- 887 108. T. Douki, *Photochem Photobiol*, 2020, **96**, 962-972.
- 888 109. T. Douki, L. Voituriez and J. Cadet, *Photochem. Photobiol.*, 1991, **27**, 293-297.
- 889 110. T. Douki, *Photochem. Photobiol.*, 2016, **92**, 587-594.
- 890 111. D. Bacqueville, T. Douki, L. Duprat, S. Rebelo-Moreira, B. Guiraud, H. Dromigny, V. Perier, S.  
891 Bessou-Touya and H. Duplan, *J. Photochem. Photobiol. B: Biol.*, 2015, **151**, 31-38.
- 892 112. C. A. Chadwick, C. S. Potten, O. Nikaido, T. Matsunaga, C. Proby and A. R. Young, *J.*  
893 *Photochem. Photobiol. B: Biol.*, 1995, **28**, 163-170.
- 894 113. P. H. Clingen, C. F. Arlett, L. Roza, T. Mori, O. Nikaido and M. H. L. Green, *Cancer Res.*, 1995,  
895 **55**, 2245-2248.
- 896 114. X. S. Qin, S. M. Zhang, M. Zarkovic, Y. Nakatsuru, S. Shimizu, Y. Yamazaki, H. Oda, O. Nikaido  
897 and T. Ishikawa, *Japanese Journal of Cancer Research*, 1996, **87**, 685-690.
- 898 115. J. A. Meador, A. J. Baldwin, J. D. Pakulski, W. H. Jeffrey, D. L. Mitchell and T. Douki, *Environm.*  
899 *Microbiol.*, 2014, **16**, 1808-1820.
- 900 116. K. Nishimura, H. Ikehata, T. Douki, J. Cadet, S. Sugiura and T. Mori, *Photochem. Photobiol.*,  
901 2020, **in press**.
- 902 117. G. Cremer-Bartels and I. Ebels, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 2415-2418.
- 903 118. H. Rokos, W. D. Beazley and K. U. Schallreuter, *Biochem. Biophys. Res. Com.*, 2002, **292**, 805-  
904 811.
- 905 119. M. P. Serrano, C. Lorente, C. D. Borsarelli and A. H. Thomas, *Chemphyschem*, 2015, **16**, 2244-  
906 2252.
- 907 120. M. P. Serrano, M. Vignoni, C. Lorente, P. Vicendo, E. Oliveros and A. H. Thomas, *Free Radic.*  
908 *Biol. Med.*, 2016, **96**, 418-431.
- 909 121. H. Yamada, T. Arai, N. Endo, K. Yamashita, M. Nonogawa, K. Makino, K. Fukuda, M. Sasada  
910 and T. Uchiyama, *Biochem. Biophys. Res. Com.*, 2005, **333**, 763-767.
- 911 122. T. M. Dreaden, J. Chen, S. Rexroth and B. A. Barry, *J. Biol. Chem.*, 2011, **286**, 22632-22641.
- 912 123. P. Walrant and R. Santus, *Photochem. Photobiol.*, 1974, **19**, 411-417.
- 913 124. S. L. Park, R. Justiniano, J. D. Williams, C. M. Cabello, S. Qiao and G. T. Wondrak, *J. Invest.*  
914 *Dermatol.*, 2015, **135**, 1649-1658.
- 915 125. A. Youssef, A. von Koschembahr, S. Caillat, S. Corre, M. D. Galibert and T. Douki, *Photochem.*  
916 *Photobiol.*, 2018.
- 917 126. P. N. Tonolli, O. Chiarelli-Neto, C. Santacruz-Perez, H. C. Junqueira, I. S. Watanabe, F. G.  
918 Ravagnani, W. K. Martins and M. S. Baptista, *J. Invest. Dermatol.*, 2017, **137**, 2447-2450.
- 919 127. N. Chouinard, J. P. Therrien, D. L. Mitchell, M. Robert, R. Drouin and M. Rouabhia, *Biochemistry*  
920 *and Cell Biology-Biochimie Et Biologie Cellulaire*, 2001, **79**, 507-515.
- 921 128. D. L. Mitchell, R. Greinert, F. R. de Gruijl, K. L. H. Guikers, E. W. Breitbart, M. Byrom, M. M.  
922 Gallmeier, M. G. Lowery and B. Volkmer, *Cancer Res.*, 1999, **59**, 2875-2884.
- 923 129. R. Berube, M. C. Drigeard Desgarnier, T. Douki, A. Lechasseur and P. J. Rochette, *J. Invest.*  
924 *Dermatol.*, 2018, **138**, 405-412.
- 925 130. M. C. Drigeard Desgarnier, F. Fournier, A. Droit and P. J. Rochette, *PLoS One*, 2017, **12**,  
926 e0173740.
- 927 131. M. C. Drigeard Desgarnier and P. J. Rochette, *DNA Repair*, 2018, **63**, 56-62.
- 928 132. S. Kimeswenger, R. Dingelmaier-Hovorka, D. Foedinger and C. Jantschitsch, *Exp. Dermatol.*,  
929 2018, **27**, 276-279.

- 930 133. P. Karran and R. Brem, *DNA Repair*, 2016, **44**, 178-185.
- 931 134. M. Guven, R. Brem, P. Macpherson, M. Peacock and P. Karran, *J. Invest. Dermatol.*, 2015, **135**, 2834-2841.
- 932
- 933 135. B. Montaner, P. O'Donovan, O. Reelfs, C. M. Perrett, X. Zhang, Y. Z. Xu, X. Ren, P. Macpherson, D. Frith and P. Karran, *EMBO Rep.*, 2007, **8**, 1074-1079.
- 934
- 935 136. K. M. Zatopek, V. Potapov, L. L. Maduzia, E. Alpaslan, L. X. Chen, T. C. Evans, J. L. Ong, L. M. Ettwiller and A. F. Gardner, *DNA Repair*, 2019, **80**, 36-44.
- 936
- 937 137. D. S. Bryan, M. Ransom, B. Adane, K. York and J. R. Hesselberth, *Genome Research*, 2014, **24**, 1534-1542.
- 938
- 939 138. M. F. Laughery, A. J. Brown, K. A. Bohm, S. Sivapragasam, H. S. Morris, M. Tchmola, A. D. Washington, D. Mitchell, S. Mather, E. P. Malc, P. A. Mieczkowski, S. A. Roberts and J. J. Wyrick, *Cell Rep*, 2020, **33**, 108401.
- 940
- 941
- 942 139. P. Mao, A. J. Brown, S. Esaki, S. Lockwood, G. M. K. Poon, M. J. Smerdon, S. A. Roberts and J. J. Wyrick, *Nature Comm.*, 2018, **9**.
- 943
- 944 140. T. A. Clark, K. E. Spittle, S. W. Turner and J. Korlach, *Genome Integr*, 2011, **2**, 10.
- 945
- 946 141. E. E. Heilbrun, M. Merav and S. Adar, *NAR Genom Bioinform*, 2021, **3**, lqab020.
- 947
- 948 142. A. Valouev, S. M. Johnson, S. D. Boyd, C. L. Smith, A. Z. Fire and A. Sidow, *Nature*, 2011, **474**, 516-520.
- 949
- 950 143. A. J. Brown, P. Mao, M. J. Smerdon, J. J. Wyrick and S. A. Roberts, *PLoS Genet*, 2018, **14**, e1007823.
- 951
- 952 144. J. Frigola, R. Sabarinathan, A. Gonzalez-Perez and N. Lopez-Bigas, *Nucleic Acids Res*, 2021, **49**, 891-901.
- 953
- 954 145. J. D. Mallet, M. M. Dorr, M. C. D. Desgarnier, N. Bastien, S. P. Gendron and P. J. Rochette, *Plos One*, 2016, **11**.
- 955
- 956 146. R. Mesa and S. Bassnett, *Investigative Ophthalmology & Visual Science*, 2013, **54**, 6789-6797.
- 957
- 958 147. J. D. Mallet and P. J. Rochette, *Photochem. Photobiol. Sci.*, 2013, **12**, 1310-1318.
- 959
- 960 148. J. D. Mallet and P. J. Rochette, *Photochem. Photobiol.*, 2011, **87**, 1363-1368.
- 961
- 962 149. A. Tewari, M. M. Grage, G. I. Harrison, R. Sarkany and A. R. Young, *Photochem. Photobiol. Sci.*, 2013, **12**, 95-103.
- 963
- 964 150. S. Del Bino and F. Bernerd, *Br. J. Dermatol.*, 2013, **169**, 33-40.
- 965
- 966 151. D. Fajuyigbe and A. R. Young, *Pigment Cell Melanoma Res.*, 2016, **29**, 607-618.
- 967
- 968 152. S. Del Bino, C. Duval and F. Bernerd, *Int J Mol Sci*, 2018, **19**.
- 969
- 970 153. T. Hore, E. Robinson and R. C. W. Martin, *World J. Surg.*, 2010, **34**, 1788-1792.
- 971
- 972 154. M. Norval, P. Kellett and C. Y. Wright, *Photodermatol. Photoimmunol. Photomed.*, 2014, **30**, 262-265.
- 973
- 974 155. S. Del Bino, J. Sok and F. Bernerd, *British J. Dermatol.*, 2013, **168**, 1120-1123.
- 975
- 976 156. D. Fajuyigbe, S. M. Lwin, B. L. Diffey, R. Baker, D. J. Tobin, R. P. E. Sarkany and A. R. Young, *FASEB J.*, 2018, fj201701472R.
- 977
- 978 157. F. Rijken, P. L. Bruijnzeel, H. van Weelden and R. C. Kiekens, *J Invest Dermatol*, 2004, **122**, 1448-1455.
- 979
- 980 158. T. Gambichler, G. Moussa, N. S. Tomi, V. Paech, P. Altmeyer and A. Kreuter, *Photochem. Photobiol.*, 2006, **82**, 1097-1102.
- 981
- 982 159. J. M. McGregor, C. A. Harwood, L. Brooks, S. A. Fisher, D. A. Kelly, J. O'Nions, A. R. Young, T. Suretheran, J. Breuer, T. P. Millard, C. M. Lewis, I. M. Leigh, A. Storey and T. Crook, *J. Invest. Dermatol.*, 2002, **119**, 84-90.
- 983
- 984 160. A. R. Young, C. S. Potten, C. A. Chadwick, G. M. Murphy, J. L. Hawk and A. J. Cohen, *J. Invest. Dermatol.*, 1991, **97**, 942-948.
- 985
- 986 161. J. M. Sheehan, N. Cragg, C. A. Chadwick, C. S. Potten and A. R. Young, *J. Invest. Dermatol.*, 2002, **118**, 825-829.
- 987
- 988 162. J. M. Sheehan, C. S. Potten and A. R. Young, *Photochem. Photobiol.*, 1998, **68**, 588-592.
- 989
163. J.-S. Taylor and C. L. O'Day, *Biochemistry*, 1990, **29**, 1624-1632.
164. M. J. Horsfall and C. W. Lawrence, *J. Mol. Biol.*, 1993, **235**, 465-471.
165. N. Jiang and J.-S. Taylor, *Biochemistry*, 1993, **32**, 472-481.
166. C. W. Lawrence, P. E. M. Gibbs, A. Borden, M. J. Horsfall and B. J. Kilbey, *Mutat. Res.*, 1993, **299**, 157-163.
167. J.-S. Taylor, *Acc. Chem. Res.*, 1994, **27**, 76-82.
168. J. E. LeClerc, A. Borden and C. W. Lawrence, *Proc. Natl. Acad. Sci. USA*, 1991, **88**, 9685-9689.
169. W. Peng and B. R. Shaw, *Biochemistry*, 1996, **35**, 10172-10181.
170. H. Ikehata and T. Ono, *J. Radiat. Res.*, 2011, **52**, 115-125.
171. N. M. Makridakis and J. K. Reichardt, *Frontiers in Genetics*, 2012, **3**, 174.

- 990 172. A. Quinet, D. J. Martins, A. T. Vessoni, D. Biard, A. Sarasin, A. Stary and C. F. Menck, *Nucleic Acids Res*, 2016, **44**, 5717-5731.
- 991
- 992 173. J. Jans, W. Schul, Y. G. Sert, Y. Rijksen, H. Rebel, A. P. Eker, S. Nakajima, H. van Steeg, F. R. de Gruijl, A. Yasui, J. H. Hoeijmakers and G. T. van der Horst, *Curr. Biol.*, 2005, **15**, 105-115.
- 993
- 994 174. U. P. Kappes, D. Luo, M. Potter, K. Schulmeister and T. M. Runger, *J. Invest. Dermatol.*, 2006, **126**, 667-675.
- 995
- 996 175. H. Ikehata, K. Kawai, J. Komura, K. Sakatsume, L. C. Wang, M. Imai, S. Higashi, O. Nikaido, K. Yamamoto, K. Hieda, M. Watanabe, H. Kasai and T. Ono, *J. Invest. Dermatol.*, 2008, **128**, 2289-2296.
- 997
- 998
- 999 176. D. E. Brash, *Photochem. Photobiol.*, 2015, **91**, 15-26.
- 1000 177. E. Sage, P. M. Girard and S. Francesconi, *Photochem. Photobiol. Sci.*, 2012, **11**, 74-80.
- 1001 178. X. Z. Tan, A. P. Grollman and S. Shibutani, *Carcinogenesis*, 1999, **20**, 2287-2292.
- 1002 179. M. A. Kalam, K. Haraguchi, S. Chandani, E. L. Loechler, M. Moriya, M. M. Greenberg and A. K. Basu, *Nucleic Acids Res.*, 2006, **34**, 2305-2315.
- 1003
- 1004 180. H. Kamiya, N. Murata-Kamiya, N. Karino, Y. Ueno, A. Matsuda and H. Kasai, *Mutat. Res.*, 2002, **513**, 213-222.
- 1005
- 1006 181. D. A. Kreuzer and J. M. Essigmann, *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 3578-3582.
- 1007 182. A. A. Purmal, Y. W. Kow and S. S. Wallace, *Nucleic Acids Res.*, 1994, **22**, 72-78.
- 1008 183. N. S. Agar, G. M. Halliday, E. S. C. Barnetson, H. N. Ananthaswamy, M. Wheeler and A. M. Jones, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 4954-4959.
- 1009
- 1010 184. N. C. Moreno, T. A. de Souza, C. C. M. Garcia, N. Q. Ruiz, C. Corradi, L. P. Castro, V. Munford, S. lenne, L. B. Alexandrov and C. F. M. Menck, *Nucleic Acids Res*, 2020, **48**, 1941-1953.
- 1011
- 1012 185. E. Sage, B. Lamolet, E. Brulay, E. Moustacchi, A. Chateaufneuf and E. A. Drobetsky, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 176-180.
- 1013
- 1014 186. D. E. Brash, J. A. Rudolph, J. A. Simon, A. Lin, G. J. McKenna, H. P. Baden, A. J. Halperin and J. Ponten, *Proc. Natl. Acad. Sci. U.S.A.*, 1991, **88**, 10124-10128.
- 1015
- 1016 187. N. Dumaz, C. Drougard, A. Sarasin and A. L. Daya-Grosjean, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 10529-10533.
- 1017
- 1018 188. A. Ziegler, D. J. Leffel, S. Kunala, H. W. Sharma, P. E. Shapiro, A. E. Bale and D. E. Brash, *Proc. Natl. Acad. Sci. U.S.A.*, 1993, **90**, 4216-4220.
- 1019
- 1020 189. L. B. Alexandrov, J. Kim, N. J. Haradhvala, M. N. Huang, A. W. Tian Ng, Y. Wu, A. Boot, K. R. Covington, D. A. Gordenin, E. N. Bergstrom, S. M. A. Islam, N. Lopez-Bigas, L. J. Klimczak, J. R. McPherson, S. Morganella, R. Sabarinathan, D. A. Wheeler, V. Mustonen, P. M. S. W. Group, G. Getz, S. G. Rozen, M. R. Stratton and P. Consortium, *Nature*, 2020, **578**, 94-101.
- 1021
- 1022
- 1023 190. L. B. Alexandrov, S. Nik-Zainal, D. C. Wedge, S. A. J. R. Aparicio, S. Behjati, A. V. Biankin, G. R. Bignell, N. Bolli, A. Borg, A. L. Borresen-Dale, S. Boyault, B. Burkhardt, A. P. Butler, C. Caldas, H. R. Davies, C. Desmedt, R. Eils, J. E. Eyfjord, J. A. Foekens, M. Greaves, F. Hosoda, B. Hutter, T. Ilcic, S. Imbeaud, M. Imielinsk, N. Jager, D. T. W. Jones, D. Jones, S. Knappskog, M. Kool, S. R. Lakhani, C. Lopez-Otin, S. Martin, N. C. Munshi, H. Nakamura, P. A. Northcott, M. Pajic, E. Papaemmanuil, A. Paradiso, J. V. Pearson, X. S. Puente, K. Raine, M. Ramakrishna, A. L. Richardson, J. Richter, P. Rosenstiel, M. Schlesner, T. N. Schumacher, P. N. Span, J. W. Teague, Y. Totoki, A. N. J. Tutt, R. Valdes-Mas, M. M. van Buuren, L. van 't Veer, A. Vincent-Salomon, N. Waddell, L. R. Yates, J. Zucman-Rossi, P. A. Futreal, U. McDermott, P. Lichter, M. Meyerson, S. M. Grimmond, R. Siebert, E. Campo, T. Shibata, S. M. Pfister, P. J. Campbell, M. R. Stratton, A. P. C. Genome, I. B. C. Consortium, I. M.-S. Consortium and I. PedBrain, *Nature*, 2013, **500**, 415-421.
- 1024
- 1025
- 1026
- 1027
- 1028
- 1029
- 1030
- 1031
- 1032
- 1033
- 1034
- 1035
- 1036 191. C. Greenman, P. Stephens, R. Smith, G. L. Dalgliesh, C. Hunter, G. Bignell, H. Davies, J. Teague, A. Butler, C. Stevens, S. Edkins, S. O'Meara, I. Vastrik, E. E. Schmidt, T. Avis, S. Barthorpe, G. Bhamra, G. Buck, B. Choudhury, J. Clements, J. Cole, E. Dicks, S. Forbes, K. Gray, K. Halliday, R. Harrison, K. Hills, J. Hinton, A. Jenkinson, D. Jones, A. Menzies, T. Mironenko, J. Perry, K. Raine, D. Richardson, R. Shepherd, A. Small, C. Tofts, J. Varian, T. Webb, S. West, S. Widaa, A. Yates, D. P. Cahill, D. N. Louis, P. Goldstraw, A. G. Nicholson, F. Brasseur, L. Looijenga, B. L. Weber, Y. E. Chiew, A. DeFazio, M. F. Greaves, A. R. Green, P. Campbell, E. Birney, D. F. Easton, G. Chenevix-Trench, M. H. Tan, S. K. Khoo, B. T. Teh, S. T. Yuen, S. Y. Leung, R. Wooster, P. A. Futreal and M. R. Stratton, *Nature*, 2007, **446**, 153-158.
- 1037
- 1038
- 1039
- 1040
- 1041
- 1042
- 1043
- 1044
- 1045 192. B. Vogelstein, N. Papadopoulos, V. E. Velculescu, S. B. Zhou, L. A. Diaz and K. W. Kinzler, *Science*, 2013, **339**, 1546-1558.
- 1046
- 1047 193. L. B. Alexandrov, S. Nik-Zainal, D. C. Wedge, P. J. Campbell and M. R. Stratton, *Cell Rep.*, 2013, **3**, 246-259.
- 1048
- 1049 194. M. Petljak and L. B. Alexandrov, *Carcinogenesis*, 2016, **37**, 531-540.

- 1050 195. C. consortium, 2020.
- 1051 196. S. Haghdoust, L. Sjolander, S. Czene and M. Hanns-Ringdahl, *Free Radic. Biol. Med.*, 2006, **41**, 620-626.
- 1052
- 1053 197. E. Hodis, I. R. Watson, G. V. Kryukov, S. T. Arold, M. Imielinski, J. P. Theurillat, E. Nickerson, D. Auclair, L. R. Li, C. Place, D. DiCara, A. H. Ramos, M. S. Lawrence, K. Cibulskis, A. Sivachenko, D. Voet, G. Saksena, N. Stransky, R. C. Onofrio, W. Winckler, K. Ardlie, N. Wagle, J. Wargo, K. Chong, D. L. Morton, K. Stemke-Hale, G. Chen, M. Noble, M. Meyerson, J. E. Ladbury, M. A. Davies, J. E. Gershenwald, S. N. Wagner, D. S. B. Hoon, D. Schadendorf, E. S. Lander, S. B. Gabriel, G. Getz, L. A. Garraway and L. Chin, *Cell*, 2012, **150**, 251-263.
- 1054
- 1055
- 1056
- 1057
- 1058 198. L. D. Trucco, P. A. Mundra, K. Hogan, P. Garcia-Martinez, A. Viros, A. K. Mandal, N. Macagno, C. Gaudy-Marqueste, D. Allan, F. Baenke, M. Cook, C. McManus, B. Sanchez-Laorden, N. Dhomen and R. Marais, *Nature Med.*, 2019, **25**, 350-350.
- 1059
- 1060
- 1061 199. J. S. Wilmott, P. A. Johansson, F. Newell, N. Waddell, P. Ferguson, C. Quek, A. M. Patch, K. Nones, P. Shang, A. L. Pritchard, S. Kazakoff, O. Holmes, C. Leonard, S. Wood, Q. Xu, R. P. M. Saw, A. J. Spillane, J. R. Stretch, K. F. Shannon, R. F. Kefford, A. M. Menzies, G. V. Long, J. F. Thompson, J. V. Pearson, G. J. Mann, N. K. Hayward and R. A. Scolyer, *Int J Cancer*, 2019, **144**, 1049-1060.
- 1062
- 1063
- 1064
- 1065
- 1066 200. X. Bonilla, L. Parmentier, B. King, F. Bezrukov, G. Kaya, V. Zoete, V. B. Seplyarskiy, H. J. Sharpe, T. McKee, A. Letourneau, P. G. Ribaux, K. Popadin, N. Basset-Seguine, R. Ben Chaabene, F. A. Santoni, M. A. Andrianova, M. Guipponi, M. Garieri, C. Verdan, K. Grosdemange, O. Sumara, M. Eilers, I. Aifantis, O. Michielin, F. J. de Sauvage, S. E. Antonarakis and S. I. Nikolaev, *Nature Genet.*, 2016, **48**, 398-+.
- 1067
- 1068 201. S. S. Jayaraman, D. J. Rayhan, S. Hazany and M. S. Kolodney, *J Invest Dermatol*, 2014, **134**, 213-220.
- 1069
- 1070
- 1071 202. S. Durinck, C. Ho, N. J. Wang, W. Liao, L. R. Jakkula, E. A. Collisson, J. Pons, S. W. Chan, E. T. Lam, C. Chu, K. Park, S. W. Hong, J. S. Hur, N. Huh, I. M. Neuhaus, S. S. Yu, R. C. Grekin, T. M. Mauro, J. E. Cleaver, P. Y. Kwok, P. E. LeBoit, G. Getz, K. Cibulskis, J. C. Aster, H. Y. Huang, E. Purdom, J. Li, L. Bolund, S. T. Arron, J. W. Gray, P. T. Spellman and R. J. Cho, *Cancer Discov.*, 2011, **1**, 137-143.
- 1072
- 1073 203. C. L. Jones, A. Degasperi, V. Grandi, T. D. Amarante, C. Genomics England Research, T. J. Mitchell, S. Nik-Zainal and S. J. Whittaker, *Sci Rep*, 2021, **11**, 3962.
- 1074
- 1075 204. N. K. Hayward, J. S. Wilmott, N. Waddell, P. A. Johansson, M. A. Field, K. Nones, A. M. Patch, H. Kakavand, L. B. Alexandrov, H. Burke, V. Jakrot, S. Kazakoff, O. Holmes, C. Leonard, R. Sabarinathan, L. Mularoni, S. Wood, Q. Y. Xu, N. Waddell, V. Tembe, G. M. Pupo, R. De Paoli-Iseppi, R. E. Vilain, P. Shang, L. M. S. Lau, R. A. Dagg, S. J. Schramm, A. Pritchard, K. Dutton-Regester, F. Newell, A. Fitzgerald, C. A. Shang, S. M. Grimmond, H. A. Pickett, J. Y. Yang, J. R. Stretch, A. Behren, R. F. Kefford, P. Hersey, G. V. Long, J. Cebon, M. Shackleton, A. J. Spillane, R. P. M. Saw, N. Lopez-Bigas, J. V. Pearson, J. F. Thompson, R. A. Scolyer and G. J. Mann, *Nature*, 2017, **545**, 175-180.
- 1076
- 1077
- 1078 205. A. H. Shain and B. C. Bastian, *Nature Rev. Cancer*, 2016, **16**, 345-358.
- 1079
- 1080 206. N. D. Sharma and R. J. H. Davies, *J. Photochem. Photobiol. B: Biol.*, 1989, **3**, 247-258.
- 1081
- 1082 207. S. Asgatay, A. Martinez, S. Coantic-Castex, D. Harakat, C. Philippe, T. Douki and P. Clivio, *J. Am. Chem. Soc.*, 2010, **132**, 10260-10261.
- 1083
- 1084
- 1085
- 1086
- 1087
- 1088
- 1089
- 1090
- 1091
- 1092
- 1093