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Advances in Brief

Mutational Inactivation of the Xeroderma Pigmentosum Group C Gene Confers Predisposition to 2-Acetylaminofluorene-induced Liver and Lung Cancer and to Spontaneous Testicular Cancer in *Trp53*$^{-/-}$ Mice[1]

David L. Cheo, Dennis K. Burns, Lisiane B. Meira, Jean Francois Houle, and Errol C. Friedberg[2]

Laboratory of Molecular Pathology, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas 75235

Abstract

Mice that are genetically engineered to mimic the human hereditary cancer-prone DNA repair-defective disease xeroderma pigmentosum (XP) are highly predisposed to UV radiation-induced skin cancer. It is not clear, however, whether XP mice or humans are predisposed to cancers in other tissues associated with exposure to environmental carcinogens. To test the importance of nucleotide excision repair in protection against chemical carcinogenesis in internal organs, we treated *XPC* mutant (*XPC*$^{-/-}$) mice with 2-acetylaminofluorene and NOH-2-acetylaminofluorene. We observed a significantly higher incidence of chemically induced liver and lung tumors in *XPC*$^{-/-}$ mice compared with normal and heterozygous littermates. In addition, the progression of liver tumors in *XPC*$^{-/-}$ *Trp53*$^{+/-}$ mice is accelerated compared with *XPC*$^{-/-}$ *Trp53*$^{+/+}$ animals. Finally, we demonstrate a higher incidence of spontaneous testicular tumors in *XPC*$^{-/-}$ *Trp53*$^{-/-}$ double mutant mice compared with *XPC*$^{+/+}$ *Trp53*$^{-/-}$ mice.

Introduction

The hereditary human disease XP[3] is characterized by defective NER of base damage that results from exposure to UV radiation and to a diverse range of chemical carcinogens (1, 2). It is therefore anticipated that this disease would confer a predisposition not only to skin cancer, as has been extensively documented (3, 4), but also to cancers of internal organs typically associated with environmental exposure (5). However, the rarity of the disease coupled with the fact that very few XP patients have been closely monitored for cancer of tissues and organs other than the skin have left this issue in considerable doubt (5). Thus, it remains unproved that humans with defective NER are indeed prone to cancer in organs other than those normally exposed to sunlight. Here we report that mice defective in the NER gene *XPC*, which are known to be highly predisposed to skin cancer after exposure to UVB radiation (6, 7), are also highly predisposed to liver and lung cancer after treatment with either AAF or its activated derivative, NOH-AAF. We also demonstrate that *XPC*$^{-/-}$ *Trp53*$^{-/-}$ double mutant mice have an increased susceptibility to spontaneous testicular tumors.

Materials and Methods

XPC mutant mice were generated previously by us (8), and *Trp53* mutant mice were purchased from The Jackson Induced Mutant Resource. Mice used in this study were generated from crosses between mice heterozygous for both *XPC* and *Trp53* (as described in Ref. 7) and consisted of all nine possible combinations of mutant and normal alleles of the two genes. Two week-old pups were either mock-treated or treated with a single i.p. injection of AAF (400 nmol/g body weight; Sigma Chemical Co.) or N-OH-AAF (200 nmol/g body weight; CCR, Inc., Chanhassen, MN) dissolved in DMSO and diluted one-tenth in tricaprylin (Sigma), as described (9). All animals were of the same strain background (75% 129/Sv, 25% C57Bl/6) and maintained under standard laboratory conditions until they were sacrificed 14–16 months after treatment for complete autopsy examination. Histological analysis was routinely performed on the lungs, liver, heart, spleen, intestine, and stomach of all animals and on any other organs in which gross pathology was noted at autopsy.

Results and Discussion

Chemically Induced Liver and Lung Tumors in *XPC Trp53* Mutant Mice. All *Trp53*$^{-/-}$ animals succumbed to spontaneous tumors frequently associated with this genotype, *i.e.*, lymphomas, soft tissue sarcomas, or testicular tumors (10), before completion of the experiment and are not included in the data sets presented here. Gross examination of the liver and lungs of animals treated with AAF or NOH-AAF revealed multiple and frequently confluent hepatic and/or pulmonary nodules of varying size and shape (Fig. 1). We typically observed multiple tumor nodules in affected organs. However, these were often confluent and precluded precise determination of the number of tumors/organ. We estimate that two to five lesions were present in every affected organ on the average. Microscopic examination of these nodules showed that they comprised either premalignant or frankly malignant lesions. The former presented as hyperplastic nodules in the liver or benign adenomas of the lung, and the latter presented as hepatocellular carcinoma or adenocarcinoma of the lung (Fig. 1). In some cases, foci of malignant change were detected in otherwise benign hyperplastic lesions. These were scored as malignant. The histological appearance of the premalignant and malignant lesions of the liver and lungs was very distinctive (Fig. 1). We did not observe lung tumors that were metastases from the liver, or *vice versa*.

Tables 1 and 2 show the proportion of premalignant hyperplastic or adenomatous and malignant lesions in the lungs and/or liver in the various genotypes examined. Results from *Trp53*$^{+/+}$ animals are shown in Table 1 and from *Trp53*$^{+/-}$ animals in Table 2. Liver and lung lesions in every affected animal are recorded in the Tables on a case by case basis. Of 17 mock-treated animals representing all six genotypes, none developed neoplastic lesions of any kind, with the exception of a single osteosarcoma in one *XPC*$^{-/-}$ *Trp53*$^{+/-}$ animal (data not shown). Because the liver and lungs represent distinct target organs, either of which can undergo AAF- or NOH-AAF-induced neoplastic change, we documented the fraction of total target organs affected in each genotype with each carcinogen. We also documented the fraction of total animals in which both the liver and lungs were affected and the fraction of total animals in which either target organ was affected in each genotype with each carcinogen.

A marked predisposition to chemically induced neoplastic change

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[2] To whom requests for reprints should be addressed, at Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX 75235-9072. Phone: (214) 648-4020; Fax: (214) 648-4067; E-mail: friedberg.errol@pathology.swmed.edu.

[3] The abbreviations used are: XP, xeroderma pigmentosum; *XPC*, xeroderma pigmentosum group C gene; NER, nucleotide excision repair; AAF, 2-acetylaminofluorene; NOH-AAF, *N*-hydroxy-2-acetylaminofluorene.

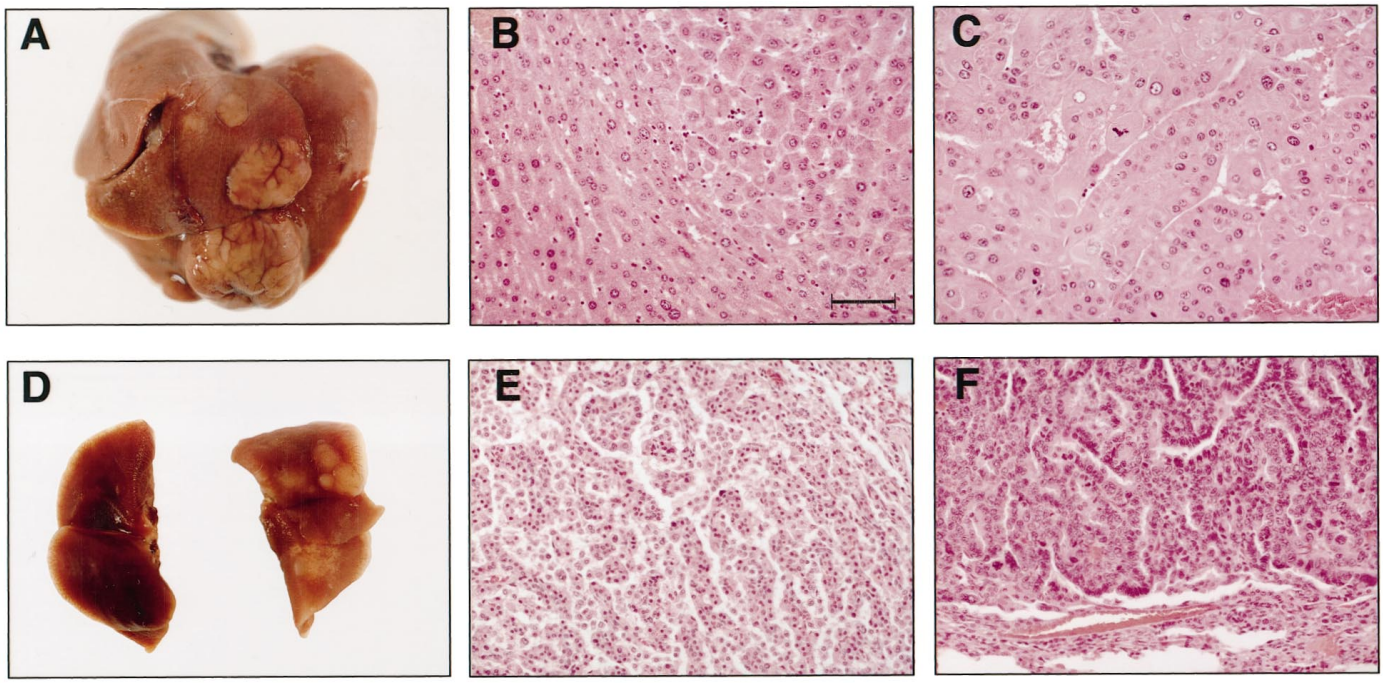

Fig. 1. Pathology of lung and liver tumors in AAF- and NOH-AAF-treated *XPC Trp53* mutant mice. *A*, gross pathology of liver tumors from an $XPC^{-/-}$ $Trp53^{+/+}$ mouse treated with NOH-AAF. Note the multiple tumor nodules of varying size. *B*, histology of the margin between normal but somewhat compressed liver tissue (*left*) and a benign nodule classified as nodular hyperplasia of the liver (*right*). C, histology of a hepatocellular carcinoma. Note the severe dysplasia and presence of mitotic figures. *D*, gross pathology of lungs from $XPC^{+/-}$ $Trp53^{+/+}$ (*left*) and $XPC^{-/-}$ $Trp53^{+/+}$ (*right*) littermate mice treated with NOH-AAF. Note the presence of multiple nodules of varying size in the lung from the $XPC^{-/-}$ animal. *E*, histology of a benign lung adenoma with a pronounced papillary pattern. *F*, histology of an adenocarcinoma of the lung. Each photomicrograph was at the same magnification. Bar, 50 μm.

Table 1 $Trp53^{+/+}$ *mice with lung and/or liver neoplasia*

XPC genotype	Treatment group	Case	Lung		Liver		Total target organs affected	Animals with both organs affected	Animals with either organ affected
			PM[a]	M	PM	M			
$XPC^{+/+}$	AAF $n = 3$	1		x			1/6 (17%)	0/3	1/3 (33%)
	NOH $n = 9$	2			x		3/18 (17%)	0/9	3/9 (33%)
		3	x						
		4			x				
	Total $n = 12$		1	1	2	0	4/24 (17%)	0/12	4/12 (33%)
$XPC^{+/-}$	AAF $n = 14$	1			x		1/28 (3.5%)	0/14	1/14 (7%)
	NOH $n = 18$	2		x	x		4/36 (11%)	1/18 (5.5%)	3/18 (17%)
		3		x					
		4			x				
	Total $n = 32$		0	2	3	0	5/64 (8%)	1/32 (3%)	4/32 (12.5%)
$XPC^{-/-}$	AAF $n = 7$	1	x		x		5/14 (36%)	2/7 (29%)	3/7 (43%)
		2		x					
		3		x	x				
	NOH $n = 8$	4	x			x	12/16 (75%)	5/8 (62.5%)	7/8 (87.5%)
		5	x		x				
		6		x	x				
		7			x				
		8	x						
		9		x	x				
		10		x	x				
	Total $n = 15$		4	5	7	1	17/30 (57%)	7/15 (47%)	10/15 (67%)

[a] PM, premalignant lesion; M, malignant lesion.

Table 2 *Trp53*$^{+/-}$ *mice with lung and/or liver neoplasia*

XPC genotype	Treatment group	Case	Lung		Liver		Total target organs affected	Animals with both organs affected	Animals with either organ affected
			PM[a]	M	PM	M			
XPC$^{+/+}$	AAF $n = 7$	1		x			1/14 (7%)	0/7	1/7 (14%)
	NOH $n = 11$	2			x		1/22 (4.5%)	0/11	1/11 (9%)
	Total $n = 18$		0	1	1	0	2/36 (5.5%)	0/18	2/18 (11%)
XPC$^{+/-}$	AAF $n = 11$	1			x		2/22 (9%)	0/11	2/11 (18%)
		2			x				
	NOH $n = 21$	3				x	5/42 (12%)	0/21	5/21 (24%)
		4				x			
		5			x				
		6			x				
		7				x			
	Total $n = 32$		0	0	4	3	7/64 (11%)	0/32	7/32 (22%)
XPC$^{-/-}$	AAF $n = 7$	1	x				6/14 (43%)	0/7	6/7 (86%)
		2		x					
		3		x					
		4		x					
		5			x				
		6				x			
	NOH $n = 5$	7		x		x	8/10 (80%)	4/5 (80%)	4/5 (80%)
		8	x			x			
		9	x		x				
		10		x		x			
	Total $n = 12$		3	5	2	4	14/24 (58%)	4/12 (33%)	10/12 (83%)

[a] PM, premalignant lesion; M, malignant lesion.

associated with the *XPC*$^{-/-}$ genotype is evident in each of the specific categories examined. As shown in Table 1 (*Trp53*$^{+/+}$ mice), we observed either premalignant or malignant lesions in 4 of 24 (17%) of the *XPC*$^{+/+}$ and 5 of 64 (8%) of the *XPC*$^{+/-}$ target organs (liver and lungs). In contrast, in the *XPC*$^{-/-}$ group 17 of 30 (57%) of the target organs were affected, indicating a clear increased susceptibility of the liver and lungs to chemically induced neoplasia.

The results were even more striking after examining the number of mice with both target organs affected. None of the *XPC*$^{+/+}$ and only 1 of 32 (3%) *XPC*$^{+/-}$ animals had lesions in both the liver and lungs. In contrast, 7 of 15 (47%) of the *XPC*$^{-/-}$ animals were so affected (Table 1). Thus, *XPC*$^{-/-}$ mice are much more likely to have lesions involving both target organs than heterozygous or normal control mice.

The increased predisposition to chemically induced liver and lung neoplasms in *XPC*$^{-/-}$ mice is also evident after examining the fraction of animals with lesions in either target organ. Among *XPC*$^{+/+}$ and *XPC*$^{+/-}$ animals, 4 of 12 (33%) and 4/32 (12.5%), respectively, developed either liver or lung lesions, whereas lesions were observed in 10 of 15 (67%) of the *XPC*$^{-/-}$ animals.

Examination of the effects of each chemical separately revealed that among the *XPC*$^{-/-}$ group, 5 of 14 (36%) of the target organs underwent neoplastic change after exposure to AAF, whereas 12 of 16 (75%) were affected by exposure to NOH-AAF. Among the group of seven *XPC*$^{-/-}$ mice with both liver and lungs affected, two of the animals (29%) were exposed to AAF, whereas five (62.5%) were exposed to NOH-AAF. Similarly, in the group of *XPC*$^{-/-}$ mice with either organ affected, the bias in favor of NOH-AAF [seven of eight animals (87.5%)] compared with AAF [three of seven animals (43%)] is repeated. Considering that twice the amount of AAF was used than NOH-AAF, these observations strongly suggest that the N-hydroxylated derivative of AAF is a more potent carcinogen.

Our conclusions that *XPC*$^{-/-}$ mice are more prone to neoplastic changes in the liver and/or lungs induced by AAF or NOH-AAF and that the N-hydroxylated is a more potent carcinogen are supported by observations with *Trp53* heterozygous mice (Table 2). Combining the results from both chemicals, only 2 of 36 (5.5%) and 7 of 64 (11%) of the target organs from *XPC*$^{+/+}$ and *XPC*$^{+/-}$ mice, respectively, were affected by neoplastic change, whereas 14 of 24 (58%) of the target organs from *XPC*$^{-/-}$ mice were affected. Similarly, none of 18 *XPC*$^{+/+}$ or 32 *XPC*$^{+/-}$ animals treated with either compound had lesions in both the liver and lungs, whereas 4 of 12 (33%) of the *XPC*$^{-/-}$ mice were so affected. Finally, 2 of 18 (11%) of the *XPC*$^{+/+}$ and 7 of 32 (22%) of the *XPC*$^{+/-}$ animals had lesions in either organ, whereas 10 of 12 (83%) of the *XPC*$^{-/-}$ mice were so affected. Examination of the effect of each chemical among the *Trp53* heterozygous mice revealed that in *XPC*$^{-/-}$ mice, 6 of 14 (43%) of the AAF-treated livers and lungs manifested neoplastic lesions, whereas 8 of 10 (80%) of the NOH-AAF-treated organs did. Additionally, none of the seven *XPC*$^{-/-}$ animals treated with AAF showed both liver and lung lesions, whereas four of five (80%) of the NOH-AAF animals were so affected.

If in the results shown in Table 1 the data from *XPC* wild type and heterozygous animals are pooled, the evidence for an increased predisposition to chemically induced cancers in *XPC* homozygous null animals is even more convincing. This conclusion is further substantiated by lumping the results from Tables 1 and 2.

Recent studies have demonstrated that *XPA* mutant mice, which are also defective in NER, are predisposed to the development of lymphomas after parenteral administration of benzo(*a*)pyrene (11). However, the lymphoid system is not a typical target site for environmental cancers in humans. AAF and its N-hydroxylated form are well characterized chemicals that affect internal organs, which are frequent targets for environmental cancer (12). These chemicals result in the

formation of N^2 and N^8 AAF guanine adducts in DNA, the removal of which is strictly dependent on functional NER in both prokaryotic and eukaryotic cells (12). The results presented here indicate that mice defective in NER are more susceptible to neoplastic changes in organs such as the liver and lungs than littermate controls. Although our results are based on a limited number of animals, our data, combined with those from *XPA* mutant mice (11), provide compelling evidence for the increased susceptibility of NER-deficient animals to chemically induced neoplasia. Hence, the failure to observe an increased incidence of tumors in organs other than the skin in XP patients likely reflects the fact that such individuals more consistently develop skin cancers associated with exposure to the highly prevalent carcinogen sunlight and die from the complications of such cancers before neoplasms associated with exposure to other environmental carcinogens can manifest. Regardless, our observations in mice may have important significance for cancer prevention in XP patients, who should be routinely counseled not only to avoid sunlight exposure but also exposure to synthetic chemicals in their diet, cigarette smoke, and other environmental carcinogens. XP heterozygous individuals should also be considered to be at increased risk because loss of heterozygosity in somatic cells is expected to predispose such cells to neoplastic transformation.

We reported previously that the latent period for the appearance of skin cancers associated with exposure of $XPC^{-/-}$ mice to UVB radiation is significantly reduced when such mice are additionally heterozygous mutant for *Trp53* (7). More recently, we have shown that $XPC^{-/-}$ $Trp53^{+/-}$ animals suffer mutations in the remaining *Trp53* allele in close to 100% of the skin cancers examined.[4] These results are consistent with those in humans, suggesting that mutational inactivation of *Trp53* is an early event in the pathogenesis of UV radiation-associated skin cancer. Interestingly, in the present study we did not observe an influence of the *Trp53* genotype on the proportion of target organs or animals affected by treatment with AAF or NOH-AAF (Tables 1 and 2). However, a comparison of the relative frequency of premalignant and malignant lesions reveals an effect of the $Trp53^{+/-}$ state on the progression of premalignant to malignant lesions in the liver. Of the 8 $XPC^{-/-}$ $Trp53^{+/+}$ animals in which neoplastic liver lesions were observed, only one (12.5%) had hepatocellular carcinoma (Table 1). In contrast, in $XPC^{-/-}$ $Trp53^{+/-}$ mice, four of six (66%) of the neoplastic livers carried hepatocellular carcinomas. This trend was also observed in $XPC^{+/-}$ animals. None of the three neoplastic livers from $XPC^{+/-}$ $Trp53^{+/+}$ mice had hepatocellular carcinoma (Table 1). However, three of seven (43%) of the livers from $XPC^{+/-}$ $Trp53^{+/-}$ animals did (Table 2).

Pooling the data from all three XPC genotypes shows that only 1 of 13 (7.7%) of the neoplastic livers harbored malignant lesions (hepatocarcinomas) in $Trp53^{+/+}$ mice, whereas in $Trp53^{+/-}$ mice, this frequency was increased to 7 of 14 (50%). In six of these seven cases, the animals were treated with NOH-AAF. These observations suggest that the progression of hyperplastic nodules of the liver to hepatocarcinomas is accelerated by loss of one *Trp53* allele, and that loss of *Trp53* function may play a role in the progression of liver cancer associated with AAF exposure. Studies are in progress to determine the fraction of hepatocellular carcinomas in which the remaining *Trp53* allele is mutated, and whether, as is the case in human liver cancer associated with aflatoxin B exposure (13), there is a hot spot(s) for mutations in *Trp53*. Interestingly, there is no indication of an effect of the *Trp53* heterozygous state on the progression of pulmonary adenomas to adenocarcinomas of the lung (Tables 1 and 2).

[4] A. M. Reis, D. L Cheo, L. B. Meira, D. K. Burns, and E. C. Friedberg, manuscript in preparation.

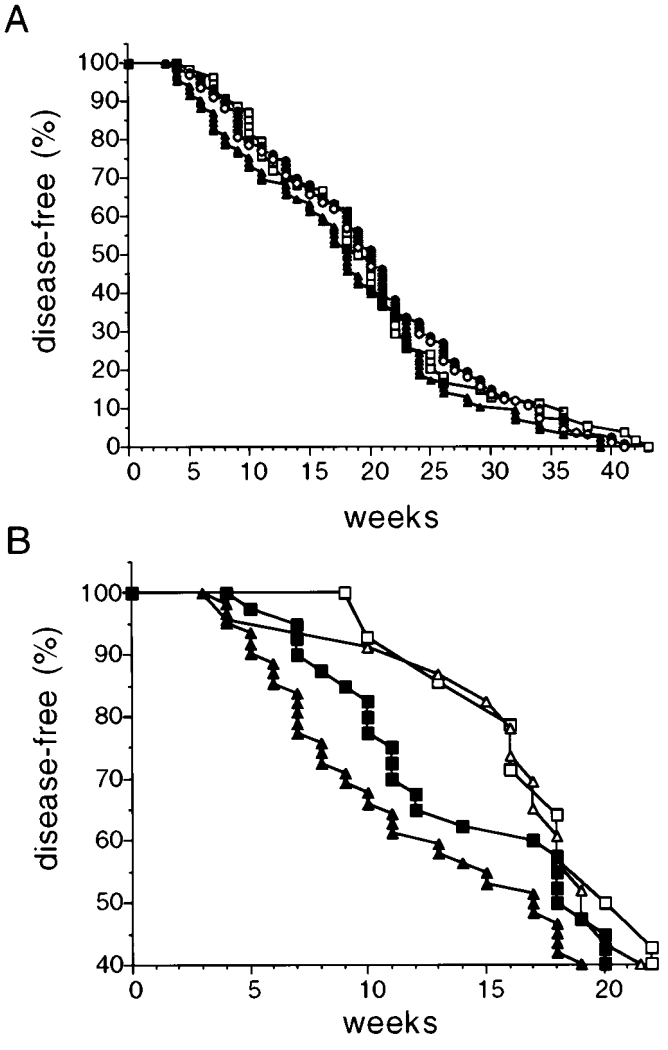

Fig. 2. Disease-free survival of *XPC Trp53* mutant mice. Cohorts of animals were observed and monitored once a week for the presence of spontaneous tumors. The fraction of animals free of signs of disease is plotted as a function of time of observation from birth. *A*, tumor development in $XPC^{+/+}$ $Trp53^{-/-}$ mice (□, 54 animals); $XPC^{+/-}$ $Trp53^{-/-}$ mice (○, 160 animals); and $XPC^{-/-}$ $Trp53^{-/-}$ mice (▲, 85 animals). *B*, analysis of tumors in male and female animals. $XPC^{+/+}$ $Trp53^{-/-}$ female mice (□, 14 animals); $XPC^{+/+}$ $Trp53^{-/-}$ male mice (■, 40 animals); $XPC^{-/-}$ $Trp53^{-/-}$ female mice (△, 23 animals); and $XPC^{-/-}$ $Trp53^{-/-}$ male mice (▲, 62 animals). Note the difference in latency for the appearance of testicular tumors between the $XPC^{+/+}$ $Trp53^{-/-}$ and $XPC^{-/-}$ $Trp53^{-/-}$ male mice.

Spontaneous Carcinogenesis in *XPC Trp53* Mutant Mice. It is well established that $Trp53^{-/-}$ and to a lesser extent $Trp53^{+/-}$ mice are highly prone to spontaneous malignancies, especially lymphomas, soft tissue sarcomas, and testicular tumors in males (10). The time course of the appearance of spontaneous tumors in $Trp53^{-/-}$ animals is indistinguishable in large cohorts of $XPC^{+/+}$ and $XPC^{+/-}$ mice (Fig. 2*A*). However, starting about 3 weeks after birth and progressing to ~22 weeks, a fraction of the $XPC^{-/-}$ $Trp53^{-/-}$ animals developed tumors slightly more rapidly than the control groups (Fig. 2*A*). Autopsy and histological examination revealed that this was exclusively the result of a higher incidence of testicular tumors (mainly teratocarcinomas) in double mutant male mice [13 of 24 (54%)] compared with $XPC^{+/+}$ [6 of 20 (30%)] and $XPC^{+/-}$ [9 of 25 (36%)] controls. This result was confirmed when the data were reduced to the period between 3 and 22 weeks after birth and segregated by sex (Fig. 2*B*). It is evident that the fraction of $XPC^{-/-}$ $Trp53^{-/-}$ mice that develop spontaneous cancers more rapidly is restricted to males. The observed increase in the number of testicular tumors in $XPC^{-/-}$ $Trp53^{-/-}$

compared with $XPC^{+/+}$ $Trp53^{-/-}$ male mice is statistically significant based on the χ^2 test ($P < 0.01$). No other *XPC*-specific differences were noted among the $Trp53^{-/-}$ or $Trp53^{+/-}$ mice with respect to either the latency or spectrum of spontaneous cancers (data not shown). It has been shown previously that the strain background can influence the frequency of testicular tumors in $Trp53^{-/-}$ mice (14). All of the animals used in this study were of identical genetic background (75% 129/Sv, 25% C57Bl/6).

Despite the fact that the $Trp53^{-/-}$ mice were not deliberately exposed to any known environmental carcinogens, it is likely that defective *XPC* function reflects defective NER, presumably of spontaneous oxidative damage. Most forms of spontaneous base damage are repaired by the base excision repair pathway (1). However, some lesions in this class (*e.g.*, thymine glycols) are known substrates for NER (15). Indeed, XP patients frequently present with neurological complications that may result from defective NER of spontaneous oxidative damage in the brain (16). It is not obvious why the testes should be a preferred site for such oxidative damage. Of course our experiments cannot formally exclude the possibility that XPC protein has an additional function(s) which is unrelated to NER, defects in which may predispose to spontaneous testicular tumors.

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