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Differences in Metabolism of Chemical Carcinogens in Cultured Human Epithelial Tissues and Cells

Curtis C. Harris, Benjamin F. Trump, Roland Grafstrom, and Herman Autrup

Laboratory of Human Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205 (C.C.H., H.A., R.G.) and Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland 21201 (B.F.T.)

The metabolism of chemical carcinogens has been studied in cultured human bronchus, colon, duodenum, pancreatic duct, and esophagus. Metabolite patterns and carcinogen-DNA adducts are generally qualitatively similar among animal species, individuals within a species, and tissues within an individual. However, wide quantitative differences are observed between individuals in outbred animal species, including humans. These interindividual differences in amounts of carcinogen-DNA adducts and in activities of enzymes that are important in the metabolism of chemical carcinogens are similar in magnitude (10-to 150-fold) to those observed in pharmacogenetic studies of drug metabolism. The role of these differences as risk factors in human cancer is being investigated.

Key words: carcinogenesis, DNA adducts, bronchus, esophagus, colon, pancreas, aryl hydrocarbon hydroxylase, N-nitrosamines, polynuclear aromatic hydorcarbons, aflatoxin, pharmacogenetics, epoxide hydrolase

Recent improvements in the conditions to culture of human epithelial tissues and cells have provided cancer researchers an opportunity to study the many facets of carcinogenesis directly in the epithelial sites of most common human cancers. Many types of tissues from adult donors can be successfully maintained in explant culture for time periods ranging from weeks to more than one year (Table I [1]). Bronchus, esophagus, colon, and pancreatic duct can also be maintained in serum-free media for several weeks. Primary epithelial cell cultures have been obtained from many different types of adult tissues. Important progress has recently been made in the development of culture conditions to support the clonal growth of human epithelial cells, eg, from the skin, bronchus, mammary gland, prostate, and esophagus. For example, human skin [2] and brochial [3] epithelial cells can be cloned and maintained in culture for 30 or more cell generations.

One important use of cultured human epithelial tissues and cells is for the study of activation and deactivation of chemical procarcinogens. There are several reasons for pursuing these studies: 1) Many environmental chemical carcinogens re-

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TABLE I. Culture and Xenotransplantation of Normal Human Epithelial Tissues and Cells*

Cancer sites	Explant	Epithelial cell culture		Xenotransplantation
		Primary	Clonal	
Breast	3[a]	+	+	+
Bronchus	12	+	+	+
Colon	0.8	+		+
Prostate	3	+	+	+
Esophagus	3	+	+	+
Bladder	4	+		+
Skin	3	+	+	+
Uterus, Corpus	2	+	+	+
Stomach	0.5			
Pancreatic duct	3	+	+	+
Uterus, Cervix	4	+	+	+

*Compiled from [1].

[a]Months in culture; tissues from adults.

quire enzymatic activation to exert their carcinogenic effects; 2) the ratio of activation to deactivation of a chemical carcinogen may determine in part an individual's susceptibility to that carcinogen; and 3) if the metabolism of a chemical carcinogen in a human tissue is the same as that found in experimental animals, the extrapolation of carcinogenesis data from these animal species to humans is more likely to be valid than if their metabolic pathways differ. Investigations of carcinogen metabolism and the use of human tissues and cells to study various aspects of carcinogenesis are being actively pursued in many laboratories throughout the world. Analysis of these studies will be reported elsewhere [4,5]. We will review here, primarily, the studies conducted in our laboratories.

MATERIALS AND METHODS

Culture of Human Epithelial Tissues

Nontumorous specimens from adult donors, with and without cancer, are collected at the time of surgery and "immediate autopsy" [6]. Specimens are transported to the laboratory in L-15 medium at 4° C. Methods have been established to culture bronchus [7], colon [8], pancreatic duct [9], and esophagus [10] in chemically defined media. After, generally, 7 days in culture to minimize the effects of exogenous agents such as drugs and dietary constituents that the donor was exposed to prior to tissue collection, the explants are incubated with carcinogens for 24 hours unless otherwise stated.

Metabolite Patterns of Chemical Carcinogens

Carcinogen metabolites are separated by chromatographic procedures [11,12]. In some cases, eg, benzo[a]pyrene, both organo soluble and water soluble metabolites have been isolated and their amounts quantified. Metabolite patterns of N-nitrosamines have been studied by measuring production of both aldehydes and CO_2 [13]

Carcinogen-DNA Adducts

The adducts derived from the metabolic activation of several radiolabeled chemical procarcinogens, ie, benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, N-ni-

trosodimethylamine, 1,2-dimethylhydrazine, have been identified by published procedures [14–17]. Binding values have also been measured by determining radioactivity bound to DNA [18], and, in the case of BP, by enzymatic radioimmunoassays [19].

RESULTS AND DISCUSSION

Procarcinogens were selected primarily on the basis that they represented several chemical classes and were found in (a) the diet, (b) drinking water, (c) polluted air, and/or (d) tobacco smoke. In addition, chemical procarcinogens of importance in experimental oncology, eg, 2-acetylaminofluorene, have been included in these studies.

The initial experimental investigations determine whether or not these chemical procarcinogens are activated by cultured human tissues into a metabolite(s) that binds covalently to DNA (Table II). Cultured human bronchus converts every procarcinogen studied to date into forms that bind to DNA. This finding indicates the wide diversity of enzymes found in the human bronchial mucosa that is a primary interface with the environment and is exposed to approximately 15,000 liters of air each day. While all of the polynuclear aromatic hydrocarbons tested were activated by all four tissue types, tissue specificity was found in the activation of N-nitrosamines. N-nitrosodimethylamine and N-nitrosodiethylamine were universally metabolized, while N-nitrosopiperidine was not detectably converted to a metabolite(s) that bound to DNA by either colon or esophagus, and N-nitrosopyrrolidine was converted by colon explants but radioactive metabolite(s) bound to DNA was not detectable in esophageal explants. In contrast, high metabolite binding values to DNA of both acyclic and cyclic N-nitrosamines were observed in cultured rat esophagus (Table III); rats are an animal species in which cyclic N-nitrosamines frequently cause carcinoma of the esophagus. Therefore, one can observe tissue specificity within an animal species, in this case humans, as well as tissue differences among animal species. Whether or not these differences are indicative, in part, of tissue susceptibility to the carcinogenic effects of N-nitrosamines remains to be determined.

Another interesting finding is that carcinogens, such as aflatoxin B_1, can be activated to carcinogen-DNA adducts by cultured human tissues—bronchus, esophagus, colon, and bladder—even though epidemiological studies have not implicated aflatoxin B_1 as a cause of cancer at these tissue sites. A simple explanation may be that epidemiology studies are not sensitive enough experimental tools to detect the associations. Alternatively, cocarcinogens may play an important role in determining cancer site, eg, induction of liver cancer by hepatitis B virus and aflatoxin B_1. Carcinogen biokinetics [20] and differential DNA repair rates [21] may also determine tissue site of cancer. Finally, it is also obvious that DNA damage is only a small fraction of the complex carcinogenic process that eventually—usually two or more decades in humans—leads to a clinically evident cancer.

Quantitative differences in binding values of carcinogens to DNA can be seen among tissue types (Table IV); the major carcinogen-DNA adducts of these carcinogens, with the exceptions of N-nitrosopyrrolidine and N-nitrosodiethylamine, have been identified [14,16,22,23]. Highest mean binding values of the polynuclear aromatic hydrocarbons and N-nitrosamines were found in the bronchus. Human colon had the highest binding levels following incubation with 1,2-dimethylhydrazine, which causes colon carcinomas in certain strains of mice and rats [24]. Analy-

TABLE II. Chemical Carcinogens Activated to Form DNA Adducts by Cultured Human Bronchus, Colon, Esophagus, Pancreatic Duct, and Bladder

Carcinogen	Bronchus	Colon	Esophagus	Pancreatic duct	Bladder
Polynuclear aromatic hydrocarbon					
benzo[a]pyrene	+[a]	+	+	+	+
7,12-dimethylbenz[a]anthracene	+	+	+	+	
3-methylcholanthrene	+	+	+		
dibenz[a,h]anthracene	+	+	+		
N-nitrosamine					
nitrosodimethylamine	+	+	+	+	
nitrosodiethylamine	+	+	+		
nitrosopyrrolidine	+	+	−		
nitrosopiperidine	+	−	−		
dinitrosopiperazine	+	+			
Mycotoxin					
aflatoxin B_1	+	+	+		+
Hydrazine					
1,2-dimethylhydrazine	+	+	+		
Aromatic amine					
2-acetylaminofluorene	+		+		+
Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole)		+			

[a]Symbols: +, carcinogen-DNA were detected; −, not detected; no symbol indicates not tested.

TABLE III. Metabolism of N-Nitrosamines by Cultured Rat Esophagus

	Formation of $[^{14}C]CO_2$[a]	Binding to DNA	
		dpm per mg DNA	pmole per 10 mg DNA
N-nitrosodimethylamine	0.54 ± 0.14[b]	3,830 ± 735 (3)[c]	380[d]
N-nitrosoethylmethylamine			1,130
[^{14}C]-Methyl	0.13 ± 0.05	4,040 ± 670 (4)	
[^{14}C]-Ethyl	1.69 ± 0.30	680 ± 120 (3)	
N-Nitrosodiethylamine	7.14 ± 0.25	1,270 ± 99 (4)	390
N-Nitrosobenzylmethylamine			
[^{14}C]Methyl	0.88 ± 0.48	19,300 ± 3,480 (4)	20,940
[^{14}C]-Benzyl	ND[e]	300 ± 430 (4)	
N-Nitrosopyrrolidine	1.14 ± 0.53	2,720 ± 270 (3)	770

[a]The results are the mean ± SD of three independent experiments; pmole [^{14}]-CO_2 per mg DNA formed per 24 hours [13].
[b]Mean ± SD.
[c]Number of individual experiments.
[d]Mean value.
[e]None detected.

sis of such composite results has obvious limitations in that not all tissue sites can be collected from each donor and not all carcinogens can be simultaneously tested. We have recently completed a study in which the metabolism of benzo[a]pyrene and formation of BPDE-DNA adducts were studied in cultured human tissues (bronchus, esophagus, colon, and duodenum) that were all collected from donors

at the time of immediate autopsy [25]. Benzo[a]pyrene metabolism and DNA binding were highest in the bronchus (Table V). No major qualitative differences in the chromatographic patterns of either water-soluble or organosoluble metabolites of benzo[a]pyrene were found among the four tissue sites. The ratio of organosoluble to water-soluble metabolites was significantly higher in colon and duodenum when compared to bronchus and esophagus. While quantitative differences were found, the distribution of the major BPDE-DNA adducts was also qualitatively similar. A positive correlation in binding values to DNA was observed among bronchus, colon, and duodenum, but the values in the esophagus did not correlate with any of the other three tissues (Table VI). In addition, no statistically significant correlations were found between DNA binding of benzo[a]pyrene or N-nitrosodiemethylamine metabolites [Autrup et al, unpublished results]. These results indicate that, in certain cases, quantitative extrapolations of carcinogen bind-

TABLE IV. Order of Mean Binding Values of Carcinogen to DNA in Cultured Human Tissues

Benzo[a]pyrene		7,12-Dimethylbenz[a]anthracene		Aflatoxin B_1		1,2-Dimethylhydrazine	
bronchus	100[a]	bronchus	100	esophagus	100	colon	100
esophagus	81	pancreatic duct	31	bronchus	61	esophagus	81
colon	20	esophagus	21	colon	11	bronchus	72
		colon	7				

Nitrosodimethylamine		Nitrosodiethylamine		Nitrosopyrrolidine	
bronchus	100	esophagus	100	bronchus	100
esophagus	67	bronchus	78	colon	52
pancreatic duct	10	colon	8	esophagus	ND
colon	6				

[a]Expressed as percentage of binding value found in tissue that has the highest mean value.

TABLE V. Metabolism of Benzo[a]pyrene by Cultured Human Bronchus, Colon, Duodenum, and Esophagus*

	Bronchus	Colon	Duodenum	Esophagus
Total metabolism[a]	65 ± 45	31 ± 27	69 ± 42	32 ± 25
organosoluble[b]	30 ± 13	71 ± 24[d]	67 ± 21[d]	43 ± 25
watersoluble[b]	72 ± 13	29 ± 23[d]	33 ± 21[d]	48 ± 33
ratio of organosoluble to watersoluble	0.4 ± 0.3	4.7 ± 8.8	5.8 ± 9.1	1.6 ± 1.6
Binding value to DNA[c]				
mean	32 ± 20	9 ± 8	18 ± 18	21 ± 20
range	4–63	1–31	2–63	2–62

*Reference [25]
[a]pMoles benzo[a]pyrene metabolites per μg DNA; mean ± SD of 15 cases.
[b]Percentage of total metabolism.
[c]pMoles benzo[a]pyrene bound per 10 mg DNA; mean ± SD of 15 cases.
[d]Significantly different from bronchus; $p < 0.05$.

ing data may be possible among some, but not all, tissues and secondly, when different chemical classes of carcinogens are compared, quantitative and predictive correlations may frequently not be observed.

Differences in carcinogen metabolism among people may be qualitative and/or quantitative. Wide quantitative differences in binding values of benzo[a]-pyrene metabolites (Table VII) and other carcinogens [4] have been found in cultured human tissues. The magnitude of these differences ranges from 50- to 150-fold and is similar to that found in pharmacogenetic studies of drug metabolism. Since benzo[a]pyrene requires three enzymatic steps to form the putative ultimate carcinogen BPDE I [(+)-(7β,8α)-dihydroxy-(9α, 10α)-epoxy-7, 8,9, 10-tetrahydrobenzo[a]pyrene] (Fig. 1), differences in the activity of these enzymes could markedly alter the rate of conversion of benzo[a]pyrene to BPDE I. The precise intracellular activities of the mixed function oxidases and epoxide hydratase responsible for the activation of benzo(a)pyrene are not precisely known.

The rate-limiting enzymatic reaction could also differ among humans and tissue types. Clues as to the range of these enzyme activities can be obtained from measurements of aryl hydrocarbon hydroxylase and epoxide hydrolase activities in subcellular fractions of these tissues. Interindividual differences in aryl hydrocarbon hydroxylase activities are substantial (Table VIII). In addition, a wide range of variation is seen among different tissues. A variation of several hundred-fold is observed in placenta and less than 20-fold in skin, kidney and bronchus. The cause(s) of the extraordinary variation of aryl hydrocarbon hydroxylase activity in placenta is unknown. Surprisingly, aryl hydrocarbon hydroxylase does not seem to be as inducible by tobacco smoke in human lung and liver. One can speculate that the

TABLE VI. Correlation of Binding Level of Benzo[a]pyrene to DNA in Bronchus, Colon, Duodenum, and Esophagus*

	r Value			
	Bronchus	Colon	Duodenum	Esophagus
p Value				
Bronchus	–	0.95	0.83	0.51
Colon	0.001	-	0.82	0.45
Duodenum	0.001	0.001	–	0.26
Esophagus	0.05	NS	NS	–

*The results are based upon 15 cases [25].

TABLE VII. Variation in Benzo[a]pyrene Binding to DNA in Cultured Human Tissues

Specimen	Interindividual variation in activity	Number of cases	Collection[a]	Reference
Bronchus	75	37	S, IA	[32]
Esophagus	99	8	S, IA	[10]
Colon	197	146	S, IA	[33]
Endometrium	70	41	S	[34]
Bladder	55	12	S, A	[35]

[a]IA, immediate autopsy; S, surgery; A, autopsy

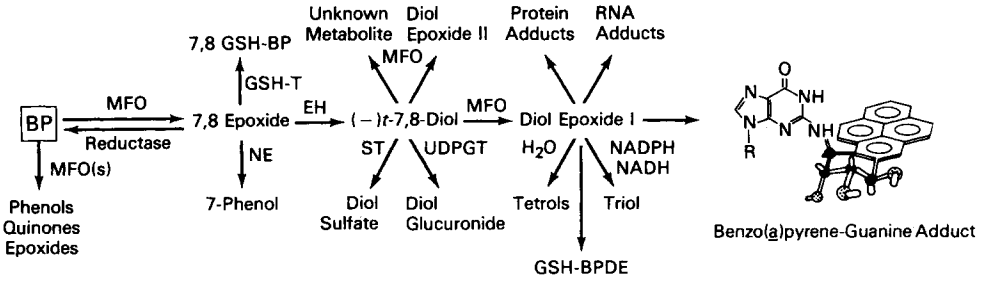

Fig. 1. Metabolic pathway of benzo[a]pyrene leading to its major DNA adduct (adapted from [27]). MFO, mixed-function oxidase; EH, epoxide hydrolase; GSH, glutathione; GSH-T, glutathione transferase.

TABLE VIII. Variation in Aryl Hydrocarbon Hydroxylase Activity in Human Tissues

Specimen	Interindividual variation in activity	Number of cases	Collection[a]	Culture	Reference
Liver	3	6	S	no	[36]
	4	26	S	no	[37]
	7	6	S	no	[38]
	14	20	S	no	[39]
	30	27	S	no	[40]
	60	15	S	no	[41]
	76	32	A,S	no	[42]
Lung	5	14	S	no	[43]
	13	13	S	no	[44]
	20	76	S	no	[45]
Bronchus	10	13	S,IA	yes	[27]
	20	10	IA	yes	[46]
Placenta	156	97	D	no	[47]
	275	21	D	no	[48]
	300	24	D	no	[49]
	350	24	D	no	[50]
Skin	3	13	S	no	[51]
	3	6	S	yes	[52]
	7	27	S	no	[53]
	7	13	S	no	[54]
Kidney	3	10	A	no	[55]
	12	23	Ab	yes	[56]

[a]A, autopsy; IA, immediate autopsy; S, surgery; D, delivery; Ab, abortion.

placenta is especially susceptible to the induction of aryl hydrocarbon hydroxylase activity by tobacco smoke and/or aryl hydrocarbon hydroxylase is already induced in the liver and lung of most nonsmokers (Table IX).

Epoxide hydrolase has lesser intertissue and interindividual differences in activity than does aryl hydrocarbon hydroxylase (Table X). One interpretation of this finding is that epoxide hydrolase has fewer isoenzymes than does aryl hydrocarbon hydroxylase. When compared to rodents, subcellular fractions of human tissues

TABLE IX. Effect of Cigarette Smoking on Aryl Hydrocarbon Hydroxylase Activity in Human Tissue and Cells

Specimen	Increase in smokers	References
Placenta	× 25	[47]
	× 40	[57]
	× 70	[48]
Liver	<2	[40]
Lung	× 2	[45]
	<2	[58]

TABLE X. Variation in Epoxide Hydrolase Activity in Human Tissues

Specimen	Interindividual variation in activity	Number of cases	Collection[a]	Culture	Reference
Liver	2	6	S	no	[36]
	8	8	A	no	[42]
	17	71	S	no	[59]
Bronchus	3	4	S	Yes	[9]
Lung	4	57	S	no	[59]
Skin	3	6	S	no	[60]
Placenta	8	21	D	no	[48]

[a]A, autopsy; IA, immediate autopsy; S, surgery; D, delivery; Ab, abortion.

have a higher ratio of epoxide hydrolase activity to aryl hydrocarbon hydroxylase activity. Although this result and those in Tables VIII–X are interesting, one should be cautious. For example, most of the studies utilized subcellular fractions that produce an aberrant pattern of benzo[a]pyrene metabolites when compared to intact cells and tissues [4,5]. Secondly, most studies did not either measure the ischemic injury that occurs with the collection of surgical and autopsy specimens or culture the intact cells and tissues to both allow reversal of this damage and minimize the effect of enzyme inducers, eg, selected drugs, that the donors were exposed to in vivo. In vitro systems will not precisely reproduce the situation at the animal level of biological organization. However, enzymatic capacity of cultured human tissues to activate many classes of chemical procarcinogens is maintained, and even under the selective pressure of monolayer cell culture, human bronchial epithelial cells actively metabolize benzo[a]pyrene up to at least 15 cell generations in vitro [3]. Finally, the mixed function oxidases in the pathway of benzo[a]pyrene metabolism (Fig. 1) may differ in their stereospecificity [29] so that the routine assay of aryl hydrocarbn hydroxylase may not be a precise indicator of benzo[a]pyrene activation, eg, activity of aryl hydrocarbon hydroxylase did not show a positive correlation with binding values of benzo[a]pyrene metabolite to DNA [26].

The exact contribution of either genetic or environmental factors in determining the activities of enzymes that lead to activation of carcinogens or those responsible for competing pathways that lead to the formation of water-soluble metabolites

is, as yet, unknown. Genetic control of wide differences in the activities of enzymes responsible for oxidation of drugs (debrisoquine, phenacetin, guanoxan, 4-methoxyamphetamine, and phenytoin) and chemical carcinogens have been observed [20,27–30]. The narrow interindividual differences found in inbred animal species when compared to outbred species, such as humans and among different inbred strains of a single animal species [31], also suggests the importance of genetic factors. Regardless of the controlling factors, these wide differences in enzymatic activities could, in part, be responsible for the wide DNA binding values of procarcinogens and individual susceptibility to the oncogenic effects of chemical carcinogens. In addition, different rates of repair of the carcinogen-DNA adducts could, in part, cause wide variations in binding values. This possibility is currently being investigated in our laboratory.

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