Abstract
The risk of developing cancer caused by environmental carcinogens lies in the balance between phase I carcinogen-activating enzymes and phase II detoxifying enzymes. Potentially genotoxic chemicals to which we are exposed to may require metabolic activation to exhibit their mutagenic and carcinogenic effects. Most of the enzyme systems, involved in carcinogen bioactivation, are concentrated in liver, but many extrahepatic organs and tissues have appreciable quantities of such enzymes. Most chemical carcinogens are activated in humans by specific cytochrome P450 (CYP) species, mainly CYP1A1, CYP1A2, CYP2E, and CYP3A. Activation of chemical carcinogens follows various metabolic pathways. The difference could range from only a single oxidation step or several sequential enzymatic steps. Polymorphic differences in carcinogen metabolism may result in difference in carcinogen risk since fast activators and/or slow detoxifiers may have higher steady state tissue concentration of the causative agent than slow activator and/or fast detoxifiers. Cancer prevention through better diet and nutrition has received considerable attention in the past and continues to show promise even today.” It has become increasingly apparent that adopting a diet may allow reduction in cancer incidence worldwide by functioning as inhibitors of tumor initiation, promotion, and progression, which may be mediated by either selective induction or inhibition of the hepatic xenobiotic metabolizing enzymes.

Key Words: Bioactivation, carcinogens, cytochrome P450, cancer prevention, hepatic enzymes

How are carcinogens assimilated in the body?
Carcinogens act through electrophilic entities which bind covalently to specific sites in DNA. Whereas some electrophilic chemicals may function as direct carcinogens, most DNA-damaging carcinogens act via formation of reactive intermediates generated by metabolic reactions in the body. A number of carcinogens, however, appear to act via mechanisms that are not related to genotoxic effect. For these diverse structure entities, no clear cut pattern of metabolic involvement is discernible. Some chemicals with promoting activity such as phorbol ester function via the un-metabolized parent compound, whereas other promoters may cause tissue proliferation by forming metabolic products (1, 2). Most of the metabolic reactions that convert chemically-stable pre-carcinogens to electrophilic, DNA-damaging species are carried out by cytochrome P450 (CYP) (3). Many forms of CYP exist with varying substrate...
specificities, organ specificities, and inter-individual difference in their distribution. Furthermore, expression of enzymes may be altered by the administration of carcinogens themselves (auto-induction), by chemical co-exposure or by nutritional influences. In addition to the CYP-mediated activation reaction, a number of other enzyme systems have been implicated in the metabolic formation of electrophilic products. These include oxidative enzyme like flavin monooxygenase (FMO), and prostaglandin H synthetase, hydrolytic enzymes such as epoxide hydrolase and carboxyl amidase, and conjugative enzymes such as glutathione-S-transferase, sulfotransferase, and acetyl transferases.

Carcinogenesis is thought to be a multistep process. This fact precludes any direct linkage between the formation of reactive intermediates, covalent binding to macromolecules, and the final outcome - uncontrolled growth. Covalent interactions of reactive intermediates with DNA may be expected to have a direct correlation with mutagenesis, except when reactive intermediates generate free radicals that cause DNA damage without covalent binding of the metabolite (4). Activation of chemical carcinogens occurs by various reactions. For some carcinogens, only a single oxidation step (aflatoxin B1, vinyl chloride) or single oxidation step followed by spontaneous chemical reaction (short chain alkyl N-nitrosamines) may be needed. For other carcinogens, different sequential enzymatic steps (polycyclic aromatic hydrocarbons) or sequential enzymatic steps followed by spontaneous reactions (2-naphthylamine) appears to be crucial (5). Most of the enzyme systems involved in carcinogen bioactivation are concentrated in liver, but many extrahepatic organs and tissues have appreciable quantities of such enzymes. Since many carcinogens induce cancer in extrahepatic tissue, those that act through reactive forms must either be converted metabolically to such forms from the parent compound or a stable metabolite in the extrahepatic tissues themselves, or they must be activated in the liver and then transported to the extrahepatic tissues. Because tumor development in most instances is dose related, it follows that, for those carcinogens that act through reactive intermediates, the sites, routes and rates of the enzymatic reactions involved may influence tumor rate. It should be realised that other steps in the carcinogenic process, such as DNA-adduct repair and promotion, may be rate-determining in the overall process.

**Carcinogen metabolizing enzymes** : Most of the xenobiots (drugs and exogenous compounds) to which humans are exposed undergo biotransformation by xenobiotic-metabolizing enzymes in the liver and extrahepatic tissues, and are eliminated by excretion as hydrophilic metabolites. Metabolic enzymes have been classified as belonging to either Phase-I or Phase-II pathways of metabolism. Phase-I biotransformations include oxidation, reduction and hydrolysis which result in the formation of functional groups and “reaction centers” on substrates. These reactions are catalyzed mainly by a super family of enzymes known as cytochrome P450 (CYP). In addition to cytochrome P450, oxidation of drugs and other xenobiotics can also be mediated by non-P450 enzymes, the most significant of which are flavin monooxygenase, monoamine oxidase, alcohol dehydrogenase, aldehyde dehydrogenase, aldehyde oxidase and xanthine oxidase (6). Phase-II biotransformations involve the conjugation of parent chemicals, or their phase-I metabolites, with small endogenous molecules such as glucuronide sulphate, glutathione, amino acids or methyl groups. Phase-I and phase-II enzymes are found most abundantly in the liver, the principal organ of biotransformation.
However, many other tissues such as the gastrointestinal tract, kidneys, lungs, skin, brain, and nasal mucosa also possess these enzymes (7). At the subcellular level, the major enzymes of biotransformation are either anchored in the membranes of the endoplasmic reticulum (P450, epoxide hydrolase, glucuronyl-transferases) or are cytosolic enzymes (aldehyde oxidase, acetyltransferases, sulfotransferases, xanthine oxidase).

Mostly, chemical carcinogens have been environmental contaminants that may be routinely ingested by humans in the diet, such as the food-derived heterocyclic amines, or less frequently chemicals given for their therapeutic value, as in the case of the synthetic estrogen, diethylstilboestrol (8). Enzymes that metabolize foreign compounds exhibit a large degree of inter-individual variability in their levels of expression (9). Inter-individual variability in drug metabolism has been shown to directly influence drug efficacy and toxicity.

The Majority of chemical carcinogens are activated in humans by specific CYP species, mainly CYP1A1, CYP1A2, CYP2E and CYP3A (10) (Table 1). Human CYP1A2 and CYP3A4 appear to be the most important enzymes with respect to activation of a number of pre-carcinogens to mutagenic species. Inter-individual susceptibility to cancer may be associated with genetic variations in these activating enzymes, and in the enzymes that catalyze detoxification of carcinogens. The highly potent hepato-carcinogen, 3-methoxy-4-aminobenzene, although selectively inducing rat CYP1A2, is itself bioactivated by rat CYP1A1.

Table 1. Major Carcinogen metabolising cytochrome P450 isozymes in human (10)

<table>
<thead>
<tr>
<th>P450 enzymes</th>
<th>Site</th>
<th>Induced by</th>
<th>Carcinogens activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 1A1</td>
<td>Extrahepatic</td>
<td>PAH, TCDD</td>
<td>BP,2-AAF AFB, 2AAF Tyro-P-2,IQ</td>
</tr>
<tr>
<td>CYP 1A2</td>
<td>liver</td>
<td>isosafrole</td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2A6</td>
<td>Liver</td>
<td>PAH</td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2B7</td>
<td>Liver</td>
<td>Phenobarbital</td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2C7</td>
<td>Live</td>
<td>Phenobarbital, Retionids</td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2C10</td>
<td>Liver</td>
<td>Phenobarbital, Dexamethasone</td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2D6</td>
<td>Liver</td>
<td>Acetone, ethanol</td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2E1</td>
<td>Liver</td>
<td></td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP 2F1</td>
<td>Liver</td>
<td></td>
<td>AFB, DEN AFB AFB AFB AFB DEN,DMN</td>
</tr>
<tr>
<td>CYP3A3</td>
<td>Liver</td>
<td>Dexamethasone, Rifampicin, Phenobarbital</td>
<td>AFB AFBBP-7 8-diol AFB IQ</td>
</tr>
<tr>
<td>CYP 3A4</td>
<td>Liver</td>
<td>Dexamethasone, Rifampicin, Phenobarbital</td>
<td>AFB AFBBP-7 8-diol AFB IQ</td>
</tr>
<tr>
<td>CYP 3A5</td>
<td>Liver</td>
<td>Dexamethasone, Rifampicin, Phenobarbital</td>
<td>AFB AFBBP-7 8-diol AFB IQ</td>
</tr>
<tr>
<td>CYP 3A7</td>
<td>Liver</td>
<td>Dexamethasone, Rifampicin, Phenobarbital</td>
<td>AFB AFBBP-7 8-diol AFB IQ</td>
</tr>
<tr>
<td>CYP4B1</td>
<td>Placenta, lung</td>
<td>Clofibrate</td>
<td>AFB AFBBP-7 8-diol AFB IQ</td>
</tr>
</tbody>
</table>

Abbreviations: AFB=AflatoxinB1; BP=Benzo[a]pyrene; 2-AAF=2-acetylamidofluorene; Trp-P-2, and IQ=food pyrolysis, mutagenic heterocyclic amines; DEN and DMN=diethyl and dimethyl nitrosamines; PAH=Polycyclic Aromatic Hydrocarbon; TCDD=tetrachloro-dibenzo-p-dioxin.

Hepatic enzymes and cancer
1A2, 2B1, 2E1 and 3A1 and by human CYP1A2, 2E1 and 3A4 (10). Aromatic amine carcinogens are preferentially activated by CYP1A2; these include 2-aminofluorene, 2-naphthylamine, 4-amino-biphenyl and several heterocyclic amines. CYP3A4 is involved mainly in the activation of carcinogens such as aflatoxins, sterigmatocystine, 2,3-dibromopropyl phosphate and several dihydrodiols of polycyclic aromatic hydrocarbons (PAH). Human CYP2E1 seems to play an important role in the oxidation of short-chain, N-alkyl nitrosamines, benzene, carbon tetrachloride, chloroform, dichloromethane, vinyl chloride, urethane, etc.

Polycyclic Aromatic Hydrocarbons: Polycyclic aromatic hydrocarbons (PAH) are commonly present in the environment as a result of industrial combustion processes and in tobacco products. Carcinogenic PAH form DNA adducts via a complex metabolic activation pathway that includes CYP1A1, whereas intermediate metabolites can be detoxified by conjugation through pathways including glutathione-S-transferase (GST). There is evidence that diol epoxides are the ultimate carcinogenic metabolite of a number of PAHs. Such epoxides are formed by three sequential catalytic reactions involving CYP and epoxide hydrolase. In rats and mice, CYP1A1 enzymes play predominant roles in both epoxidation reactions and benzo[a]pyrene activation (11). Whereas the initial oxidation of benzo[a]pyrene is catalyzed by CYP1A1, further activation is performed by CYP3A4 in human liver (Fig. 1). Cigarette smoke contains a wide variety of polycyclic hydrocarbons (Table 2), nitrosamines, and aromatic amines. There is a highly significant correlation between the amount of immunoreactive CYP and high affinity component of phenacetin-\(O\)-deethylase (CYP1A2) activity in both smokers and non-smokers. A dramatic increase of benzo[a]pyrene hydroxylation in human placenta is also seen in smokers (12). 6-Nitrochrysene is present in environmental sources such as diesel exhaust particulate and has been shown to be a potent liver and lung carcinogen in newborn mice. The formation of proximate carcinogen trans-1,2-dihydro-1,2-dihydroxy-6-nitrochrysene is the most abundant metabolite of 6-nitrochrysene in human microsomes, and is preferentially catalysed by CYP1A2 (13).

Arylamines: Humans are frequently exposed to arylamines such as 2-naphthylamine and 4-aminobiphenyl, found in coal and shale-derived oils and in agricultural chemicals. 4-aminobiphenyl is regarded as the most potent of the arylamine human pro-carcinogens and is primarily activated by CYP1A2 to a reactive hydroxylated metabolite that can enter the circulation and be transported to the urinary bladder where reabsorption into the bladder epithelium and arylamine-DNA adduct formation can occur (14).

Aromatic amines: 2-Acetylaminofluorene (AAF) is a model carcinogenic aromatic amine. This shows considerable species difference with respect to hepato-carcinogenecity. Rats are much more susceptible than mice or hamster whereas guinea pig has been found resistant (15). It is extensively metabolised by human liver microsomes, and is activated by N-hydroxylation to ultimate carcinogen.

Nitrosamines: Nitrosamines require metabolic activation to initiate the carcinogenic response. For example, nitrosodimethylamine (NDMA) is hydroxylated by CYP at its a-carbon atom to yield an unstable metabolite, which decomposes to give a reactive metabolite (16). Of 11 reconstituted mono-oxygenase systems containing individual purified rat P450 enzymes, only CYP2E1 has high activity for N-demethylation of NDMA (17). Human CYP2E1
also appears to play an important role in the metabolic activation of NDMA and other short chain nitrosamines.

**Mycotoxins:** The mycotoxin, aflatoxin B₁ is a very potent liver carcinogen in rats. Metabolic activation of aflatoxin B₁ appears to be one step oxidation reaction to form the epoxide. In human, rat, and hamster, the major CYP enzymes involved in aflatoxin activation are CYP3A4, CYP1A2, CYP2C11 and CYP2A3, respectively (18). CYP1A2 has also been found to be primarily responsible for activation of aflatoxin B₁ under ordinary conditions of human exposure. Aflatoxin B₁ is produced by some strains of Aspergillus, which grow on a variety of agricultural products, such as peanuts. Numerous outbreaks of human acute aflatoxicosis involving liver failure and gastrointestinal bleeding have occurred in Southeast Asia and Africa.

**Food Mutagens:** Epidemiological studies have revealed a strong association between diet and a variety of human cancers. Heterocyclic aromatic amines (HAAs) are formed when meat juices are pyrolyzed. In humans, HAAs are activated in vivo by CYP1A2 and N-acetyltransferase (NAT) to mutagens or carcinogens (19). While activity of NAT is non-inducible, exposure to cruciferous vegetables containing indole-3-carbinol, caffeine, and some forms of green tea have been shown to induce CYP1A2 activity in humans.

**Variations in Carcinogen Metabolism**

**Polymorphism:** Polymorphic differences in carcinogen metabolism may result in difference in carcinogen risk since fast activators and/or slow detoxifiers may have higher steady state tissue concentration of the causative agent than slow activator and/or fast detoxifiers. There is some evidence that differences in cancer risk are related to polymorphic variations in P450 N-acetyltransferase or glutathione transferase enzymes (20, 21). Similarly, for PAH-DNA (polycyclic aromatic hydrocarbon–DNA) adducts in white blood cells, the range of binding levels was 3-9 fold among smokers and 2-7 fold among non-smokers (22, 23).

**P450 enzyme content:** Changes in CYP composition can influence tumor initiation in experimental animal systems. Indirect evidence for role of CYP is provided by experiments in which in vitro mutagenesis and DNA adduct formation are affected by changes in CYP composition, which can be brought about by genetic means or by enzyme induction with reconstituted purified enzymes (24). Although increases in CYP enzyme activity occur in liver and extrahepatic tissue of genetically-responsive mice, only extrahepatic tissues show enhanced tumor formation and these experiments have been restricted to PAH. Most of the PAHs were used in single dose complete carcinogen bioassays, and the possibility must be considered that their effect might not only be on initiation. Any experiments designed to show roles of enzymes in tumor initiation must be carefully constructed to show that the enzyme inducers are truly acting as co-carcinogens and not as promoters (some barbiturates and hydantoins are inducers but not promoters).

**Tumor promoters:** Tumor promoters are chemicals which increase the number of tumors when administered after initiating carcinogens at doses which, by themselves, do not produce tumors, and are distinguished from co-carcinogens, which must be administered very close to the time of initiation. There is a possibility that the formation of electrophilic metabolites of carcinogens can play a role in their tumor-promoting activities (25).

**Non-hepatic P450 enzymes:** In some extrahepatic tissues CYPs are highly localized in particular regions or cell types so that local Aflatoxins, which grow on a variety of agricultural products, such as peanuts. Numerous outbreaks of human acute aflatoxicosis involving liver failure and gastrointestinal bleeding have occurred in Southeast Asia and Africa.

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**Non-hepatic P450 enzymes:** In some extrahepatic tissues CYPs are highly localized in particular regions or cell types so that local Hepatic enzymes and cancer
concentration may approach that found in liver. These tissue specific differences in CYP can be major determinants in extrahepatic carcinogenesis, since these CYPs can activate chemicals in close proximity to targets. On the other hand, evidence exists that some of the ultimate carcinogens can migrate throughout the body. It should also be pointed out that, in extrahepatic tissues, high levels of FMO and prostaglandin synthase can be found. Often these enzymes form the same products that are encountered in CYP reactions, and caution should be exercised in assignment of the various enzymes.

**Dietary influence:** Food contains a variety of specifically healthful or harmful components and hence the incidence of cancer has a strong relationship to the food we ingest. The knowledge of nutrition’s role in the pathogenesis of cancer has recently continued to increase with evidence coming from ecological correlation, particularly in the United States, and Japan, where several types of cancer differ greatly in its incidence (27).

A variety of highly sensitive analytical techniques can detect food-borne carcinogenic chemicals. Aflatoxins, which are potent carcinogenic mycotoxins produced by fungi, were not discovered until 1960, but were probably at significant levels in certain crops such as corn or peanuts prior that time (28). Aflatoxins have been associated with liver cancer in Asian and African countries, where exposure is high, and chronic hepatitis also contributes. During the cooking of food, a variety of heterocyclic amines are formed in the browning reactions (29). These DNA–reactive agents are potent multi-organ and multi-species carcinogens, in many species including primates. It has been postulated that they may be the initiating agents for breast, prostate, pancreas, and colon cancers in western societies (30).

**Table 2.** Examples of polycyclic hydrocarbons (PAH) present in cigarette smoke (40)

<table>
<thead>
<tr>
<th>3,4-Benz[a]pyrene</th>
<th>Naphthalene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibenzo[a,e]pyrene</td>
<td>Acenaphthene</td>
</tr>
<tr>
<td>Dibenzo[a,h]anthracene</td>
<td>Acenaphthene</td>
</tr>
<tr>
<td>1,2-Benzanthracene</td>
<td>Fluorene</td>
</tr>
<tr>
<td>1,2,5,6-Dibenzanthracene</td>
<td>Phenanthrene</td>
</tr>
<tr>
<td>Chrysene</td>
<td>Fluoranthene</td>
</tr>
<tr>
<td>3,4-Benzofluorene</td>
<td>Pyrene</td>
</tr>
<tr>
<td>Anthracene</td>
<td>Benzo[b]fluoranthene</td>
</tr>
<tr>
<td>Cyclophenta[c,d]pyrene</td>
<td>Perylene</td>
</tr>
<tr>
<td>Indeno[1,2,3-cd]pyrene</td>
<td>Coronene</td>
</tr>
</tbody>
</table>
| Benzo[ghi]perylene| Cinoy Maliakal *et al*
Consumption of well-done red meat, a source of heterocyclic amines, has been associated with an increased risk of colorectal adenomas, (precursors of carcinomas). In the stomach, nitrosation reactions involving nitrates and other components in the diet give rise to nitrosamides and nitrosamines. These carcinogens are postulated to be initiating agents for stomach and esophageal cancer. Among beverages, alcohol consumed in excessive amounts is clearly associated with liver disease and increased risk of liver cancer, as well as esophageal cancer linked with cigarette smoking. Increased risk of colon cancer is also reported to be associated with alcohol consumption. Coffee has also been discussed as a risk factor, particularly for bladder cancer, but a causal association has not been established. In fact, caffeine may possibly be antimutagenic (31).

Prevention of Cancer: Early diagnosis, novel therapy as well as cancer chemoprevention is needed, if the battle against cancer is to be won. Chemoprevention in recent years has emerged as a potential strategy for control of cancer. Chemoprevention is a means by which the use of naturally-occurring and/or synthetic compounds completely prevents, blocks or reverses occurrence of the disease (32-34). Cancer chemoprevention is also defined as the prevention, inhibition, or reversal of carcinogenesis by administration of one or more chemical entities, either as individual drugs or as naturally-occurring constituents of the diet. Cancer prevention through better diet and nutrition has received considerable attention in the recent past and also promises to be a particularly important issue now. In this new millennium it has become increasingly apparent that an era where the option of adopting a diet that may allow reduction in cancer incidence worldwide has been entered. Almost one third of cancers are caused by dietary substances and the strategy of manipulation of diet is being increasingly recognized as a practical approach for cancer prevention. It is one of the novel approaches of controlling cancer by alternative therapy that has some limitations and drawbacks in patient treatment. It is important to find a way to neutralize carcinogens or protect against deleterious effects they exert. In this respect, chemoprevention offers a realistic promise to reducing the incidence of human cancer.

For many chemopreventive agents, mechanistic details of how they act are not fully elucidated. Many agents may act through more than one mechanism, making it difficult, if not impossible, to establish the most effective mode of action. Conventional classification of chemopreventive agents is based on the underlying mechanism by which they exert protective effects on a specific stage of multi-step carcinogenesis, where tumor development has been generally considered to consist of three distinct steps-initiation, promotion, and progression. Chemopreventive agents may be classified as inhibitors of carcinogen formation, blocking agents and suppressing agents. Blocking agents are inhibitors of tumor initiation, while suppressing agents are inhibitors of tumor promotion/progression. Inhibitors of Carcinogen formation predominantly prevent the formation of nitrosamines from amine and nitrite in an acidic medium. These inhibitors of carcinogen formation include reductive acids like ascorbic acid, phenolic compounds like caffeic acid, gallic acid, sulfhydryl compounds such as N-acetylcysteine and amino acids like proline (35-37). Blocking agents act by chemical intervention at the initiation stage of carcinogen. They could be classified as inhibitors of CYP enzymes; inducers of CYP enzymes; inducers of phase-II enzymes or scavengers of electrophiles and free radicals; inducers of DNA repair. Suppressing agents can be classified as compounds that inhibit Hepatic enzymes and cancer.
polyamine metabolism; induce terminal cell differentiation; modulate signal transduction; modulate hormonal/growth factor activity; inhibit oncogene activity; promote intercellular communication; restore immune response; induce apoptosis; correct DNA methylation imbalance; inhibit basement membrane degradation; and inhibit arachidonic acid metabolism (38, 39).

**Conclusion**

Modulation of carcinogen metabolism is often considered by many investigators as a mechanistic basis for protective effect of many types of chemopreventive phytochemicals in the initiation stage of carcinogenesis. However, inhibition of initiation alone is less of a practical approach to chemoprevention, since there are diverse types of initiators present in environment. It is not feasible to find a chemopreventive agent that can nullify the initiating activity of all carcinogens to which humans are exposed. Therefore, recent chemopreventive strategies are more concerned with identifying substances with anti-proliferative or anti-progressive activity that can suppress transformation of initiated or precancerous cells to malignant ones. More studies should investigate the mechanisms which include modulation of signal transduction, inhibition of oncogene activation, inhibition of polyamine metabolism, inhibition of angiogenesis etc. Judicious utilization of current advances in molecular biology and tissue culture techniques would help achieve this objective more quickly. It is widely agreed that conducting intervention trials of chemopreventive agents on human cancer is an important approach to elucidate any protective effect. It is important to know the levels of putative active components in target tissues and whether such levels are capable of inhibiting cancer formation and growth.

![](image)

**Fig. 1.** Metabolism and activation of polycyclic aromatic hydrocarbons. Metabolic enzymes cytochrome P450 (CYP1A, CYP3A4) and microsomal epoxide hydrolase (EH) activate Benzopyrene to BP-diol-epoxide that forms stable DNA adducts leading to carcinogenesis.

**References**


