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A Review of Polyamines and Cancer

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History – All Things Living

The first research publication describing polyaminated compounds in cancer tissues occurred in 1958 in the Proceedings of the National Acadamy of Japan (1). In those early years, polyaminated molecules and substances were identified in all forms of life – bacteria, fungus, plants, and all types of eukaroytic cells. They were determined to be critical for all types of cellular proliferation, and indeed for the continuation of life in all currently known cell types. Immediately, research on polyamines expanded very rapidly. Between 1960 and 1985, there were more than 5,000 research publications about polyaminated small molecules and compounds, including 11 multi-chapter research review books (2-12) and six extensive review publications (averaging more than 50 pages per review) just by the Tabors alone (13-18). It was anticipated that knowledge and/or control of intracellular polyamine systems would have unlimited industrial and medical/clinical applications. However, now 45 years later, these great expections have not proven to be "exactly" correct.

Polyamine Structures and Metabolic Pathways

During the 1960s and 70s most polyamine research was focused upon elucidating the molecular structures of the various polyaminated molecules and determining the metabolic pathways of synthesis and degradation (10-12,17-18). During these early years it soon became obvious that there were several natural biologically active polyaminated molecules (in addition to lysine/arginine rich histones) in various forms of life. And that they might differ in plants, prokaryotes and eukaryotes. This review will focus only upon eukaryotic life forms, specifically mammalian normal and cancer cells/tissues.

The major natural, biologically active polyamines identified in mammalian cells/tissues include putrescine (PUT), spermidine (SPD), spermine (SPM), and possibly some of the polyamine metabolites such as N-acetyl spermidine (N-acetyl SPD), N-acetyl spermine (N-acetyl SPM), and hydrogen peroxide (H2O2). The three major polyamines in mammalian cells are synthesized in sequence from ornithine to PUT (2+) to SPD (3+) to SPM (4+) (Figure). Each of them are small, straight chain aliphatic water soluable carbon-nitrogen molecules with the amino groups evenly distributed throughout. The first critical step is the synthesis of PUT by the decarboxylation of ornithine, which is accomplished by the rate limiting enzyme of the pathway, ornithine decarboxylase (ODC). This is followed by the conversion of S-adenosylmethionine (SAM) to decarboxylated S-adenosylmethionine (DAM) by S-adenosylmethionine decarboxylase (SAMD). DAM is added to PUT by SPD synthetase to produce SPD. A second DAM is then added to SPD by SPM synthetase to produce SPM. Catabolism of the latter two polyamines occurs via a single enzyme, SPD/SPM acetyltransferase (SSAT). The latter enzyme converts SPD and SPM to N-acetyl-SPD and N-acetyl-SPM, respectively. Further catabolism may occur via polyamine oxidase, which converts N-acetyl-SPD and N-acetyl-SPM to putresine and SPD, respectively, and yields H2O2 and acetoamidopropanol (ap) (9-12,16-20).

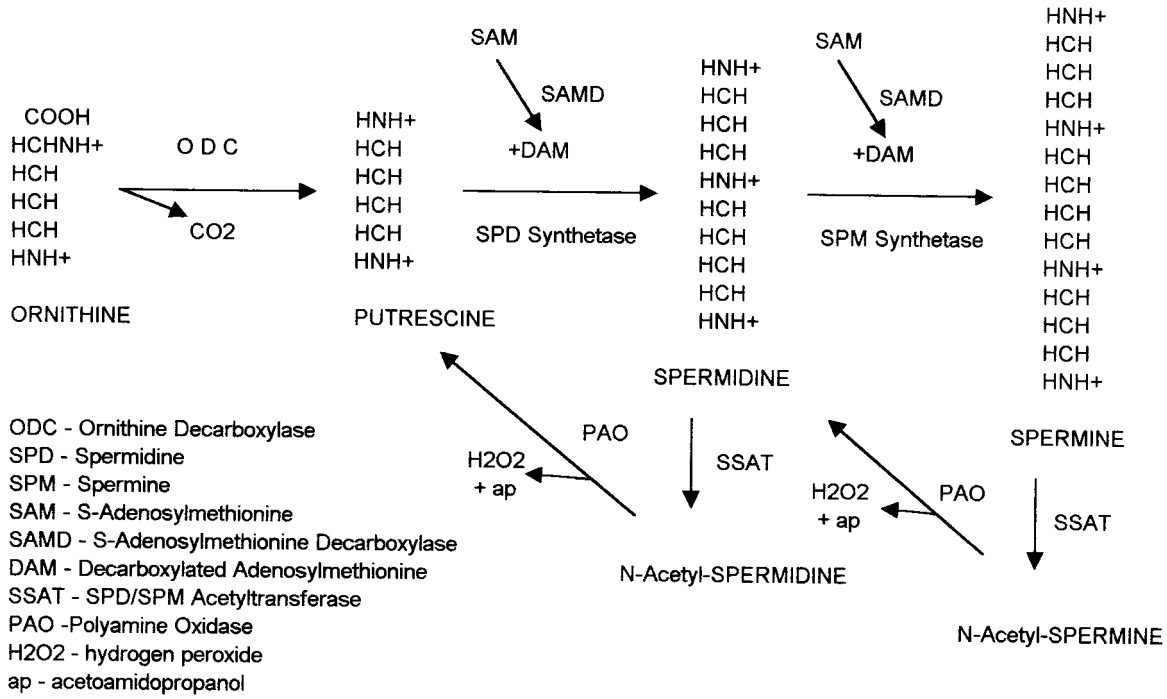

Figure. Biosynthesis of Polyamines.

Key Enzymes of Polyamine Biosynthesis

The key enzymes in the biosynthesis and catabolism of polyamines in mammalian cells are well understood (5-20). The first critical and rate limiting enzyme in the polyamine biosynthetic pathway is ODC (7-18). The ODC gene can be induced by hormones in certain cell types and by the cancer oncogene protein product, the myc oncoprotein. It has a very rapid turnover rate (only a few minutes), and it is located in both the cytoplasm and the nuclei of mammalian cells. Therefore, the polyamine system is compartmentalized and may play different roles in the cytoplasm versus the nucleus. Because ODC is the first pathway enzyme, is rate limiting, and has a short half life, it is a logical target for drug control. Over the past 40 years hundreds of research papers have focused upon this enzyme in attempts to control cellular growth processes, especially in cancer cells/tissues.

The next most important biosynthetic enzyme is SAMD, which converts SAM to DAM. This enzyme is constitutive and is stimulated by putrescine. Drug inhibitors of SAMD inhibit the proliferation of many cell types.

The final two synthesis steps involve SPD synthetase and SPM synthetase. These enzymes are constitutive and apparently are not involved in any cellular regulatory control actions.

The first catabolic enzyme in the polyamine biosynthetic pathway is SSAT. This enzyme converts both SPD and SPM to N-acetyl-SPD and N-acetyl-SPM, respectively. SSAT is inhibited, activated and/or induced by a variety of metabolites and synthetic polyamine derivatives. Stimulation of SSAT decreases polyamine levels and inhibits the proliferation of many cell types.

The second major enzyme in polyamine catabolism is POA. This enzyme converts N-acetyl-SPD and N-acetyl-SPM to PUT and SPD, respectively. During these catabolic steps, H2O2 and acetoamidopropanol are given off as reaction products. These latter metabolites may play a role in stimulating cellular apoptosis (to be described later).

Drug Inhibitors

Early in the research efforts on the elucidation of the structures of the natural, biologically active polyamines and their synthetic and catabolic pathways, ODC was determined to be the key rate limiting and rate controlling enzymatic step in mammalian cells. In the 1970s, difluoromethylornithine (DFMO) was established

to be a very potent mechanism based (suicide – not reversible) inhibitor of ODC (7-11,19-20). DFMO has been used extensively over the past 30-40 years during research on the establishment of the synthesis and the catabolism of the polyamine pathways, the evaluation of the polyamine controlled mechanisms involving cell proliferation and differentiation, the inhibition of cancer cell growth, the enhancement of existing human cancer therapies, the development of new cancer chemotherapy approaches, and even in cancer prevention programs. Polyamine pathway related drugs, including polyamine derivatives, and their enzyme targets are given in Table 1 (19-35).

During the past 20-25 years several hundred polyamine synthesis inhibitors, polyamine catabolism stimulators, and other polylamine derivatives have been tested by computer simulation analysis and on isolated purified enzymes, with subcellular fractionations, in tissue culture (normal and cancer cells), in intact laboratory animals (normal and cancer cells), and in cancer patients in experimental clinical trials (19-39). These drugs have focused on the key polyamine biosynthetic enzymes, catabolic enzymes, polyamine uptake/transport systems, and various downstream DNA, RNA, proteins and enzymes, and specific regulatory control systems. Most of the research has focused upon attempts to decrease cancer cell growth by decreasing the intracellular levels of PUT, SPD, and SPM. Such efforts have resulted in numerous cytostatic and/or cytotoxic actions in various cell types (20-27) and Table 1.

Inhibitors of the key enzymes in polyamine biosynthesis include DFMO, MAP, MGBG, and AdoData (see Table 1). Combinations of these four drugs decreased polyamine levels 60 to 90% in many cell types, slowed the proliferation of target cells, but rarely inhibited cell growth to 100%. Most mammalian cells, including cancer cells, have membrane localized polyamine uptake/transport systems. When the polyamines decrease inside a cell, these systems import polyamines from neighboring cells and the blood vascular system. The importer systems take up natural polyamines and many synthetic polyamine derivatives. Hence the presence of polyamine uptake/transport systems are being used in two ways in cancer therapy: 1) to inhibit the systems and prevent uptake of natural polyamines, 2) to allow the systems to be increased by intracellular polyamine depletion and then give potent polyamine

Table 1. Inhibitors/Activators of Polyamine Related Enzymes

ORNITHINE DECARBOXYLASE
DFMO – α-difluoromethylornithine (-)
MFMO – α-monofluoromethylornithine (-)
MAP – (2R,5R)-δ-methylacetylenicputrescine (-)
DENSpm – N^1,N^{11}-diethylnorspermine (-); also known as DE-3-3-3
BESpd – N^1,N^8-bis(ethyl)spermidine (-)
E-α-fluoromethyl-dehydroornithine methyl ester (-)
R-α-ethynyl-(R)-δ-methylputrescine (-)
antizyme protein (-)

S-ADENOSYLMETHIONINE DECARBOXYLASE
DENSpm – N^1,N^{11}-diethylnorspermine (-)
MGBG – methylglyoxal bis (guanylhydrazone) (-)
EGBG – ethylglyoxal bis(guanylhydrazone) (-)
DEGBG – diethylgloyxal bis(guanylhydrazone) (-)
MHZPA – S(5'-deoxy-5'-adenosyl) methylthioethylhydroxylamine (-)
MAOEA – 5-deoxy-5'[N'-methyl-N{2-(aminooxy)ethyl}]aminoadenosine (-)

SPERMIDINE SYNTHETASE
AdoDato – S-adenosyl-1,8-diamino-3-thiooctane (-)
AdoDatad – S-adenosyl-1,12-diamio-3-thio-azadodecane (-)
AdoS+$(CH_3)_2$ – S-methyl-5'-methylthioadenosine (-)
4MCHA – trans-4-methylcyclohexylamine (-)
n-butylalmine (-)
cyclohexylamine (-)

SPERMINE SYNTHETASE
AdoDato; AdoDatad; AdoS$^+(CH_3)_2$ from above (-)
BDAP – N-(n-butyl)-1,3-diaminopropane (-)
APCHA – N-(3-aminopropyl)cyclohexylamine (-)

SPD/SPM ACETYLTRANSFERASE
DENSpm – N^1,N^{11}-diethylnorspermine (+)
BENSpm – N^1,N^{11}-bis(ethyl)norspermine (+)
BESpm – N^1,N^{12}-bis(ethyl)spermine (+)
BESpd – N^1,N^8-bis(ethyl)spermidine (+)
BEHSpm – N^1,N^{14}-(ethyl)homospernine (+)
CPENSpm – N^1-ethyl-N^{11}[(cyclopropyl)methyl]-4,8-diazaundecane (+)

POLYAMINE OXIDASE
Aminoguanidine (-)
Pargyline (-)
MDL 72527 – N^1,N^4-bis(2,3-butanedienyl)1,4-butanediamine (-)
MDL 72521 – N^1-methyl-N^2-(2,3-butadienyl)-1,4-butanediamine (-)
Oxa-spermine derivatives (+)

POLYAMINE CELLULAR UPTAKE AND TRANSPORT SYSTEMS
antizyme protein (-)
DENSpm – N^1,N^{11}-diethylnorspermine (+)
MQT 1426 – D-lysine-spermidine (-)

OTHERS WITH UNESTABLISHED MOLECULAR MECHANISMS
BE-4-4-4-4 – 1,19-bis-(ethylamino)-5,10,15-triazanonadecane; a pentamine
BE-3-7-3 – N,N'-bis[3-(ethylamino)-propyl]-1,7-heptanediamine
BE-3-4-3 – N^1,N^{12}-diethyl spermine
BE-4-4-3 – 3,7,12,17-tetra-azanonadecane[N^1,N^{13}-diethyl(amiopropyl)homo spermidine]
BE-4-4-4 – N^1,N^{12}-diethylhomospermine
1,12-diaziridinyl-4,9-diazodecane
Dimethylsilane tetramines as SPM analogues
Finasterides
Amifostine derivatives
Platinum SPD analogues
Fluorescent polyamine analogues

derivatives that can be taken up in high quantity into the cancer cell and that can then interfere or block key cell proliferation events (29,31,35-39).

Several stimulators of the polyamine catabolic enzymes have been developed including BENSpm, BESpd, and BEHSpm (see Table 1). Stimulation of the degradation of the polyamines can decrease intracellular levels of polyamines and slow cell proliferation 60-85% (19-22,25-26,36-37).

However, to obtain 100% inhibition of cancer cell proliferation in vivo, a combination of polyamine synthesis inhibitors and polyamine catabolic stimulators, and possibly cell uptake/transport blockers, are often required. For example, the combination of DFMO and MGBG, which has been studied in tissue culture, animal models, and human clinical trials, is very successful at inhibiting cancer cell growth. DFMO inhibits ODC, depleting cells of polyamines. Subsequent treatment with a polyamine derivative, such as MGBG, which can be rapidly transported and which inhibits SAMD, can be very effective in inhibiting most types of cancer cell proliferation up to 99% in culture, and more than 95% inhibition of transplanted cancers in animals (19-22,25-26,35-42).

Because the natural polyamines are small, completely water soluble, aliphatic carbon chains with multiple positive charges, they bind both specifically and non-specifically to numerous macromolecules such as DNAs, RNAs, membrane proteins, soluable proteins, and enzymes, and many small, negatively charged polyphosphorylated molecules in the cytoplasm and nucleus. Therefore, direct and specific molecular functionings of the polyamines are not yet understood, almost 50 years after their discovery. When a *specific* binding of polyamines to a macromolecule and subsequent *modification of the function* of that macromolecule is observed, new polyamine derivatives are synthesized and studied. Utilization of these latter drugs, plus use of the earlier described drug efforts on polyamine biosynthetic pathway enzymes, may be more effective in both cytostatic and cytotoxic efforts on cancer cells. Such "downstream" polyamine specific targets will be described later.

Cellular Mechanisms

Polyamines are required for optimal growth in all known types of biological cells. In most cells, loss of these polyamines results in inhibition of cell proliferation and differentiation, and sometimes cell death (necrosis and/or apoptosis). In addition, most studies with mammalian cells showed that when quiescent cells were stimulated to grow the levels of ODC and intracellular polyamines increased before increases occurred in DNA, RNA, and proteins (19-20,36,38-42). However, just which specific molecular systems are being stimulated (or de-inhibited), first, and in what sequence, has yet to be determined. Many studies show that the polyamines are also directly linked to cellular proliferation, differentiation, and cell death. Current working theories concerning polyamine regulation of intracellular macromolecular events in mammalian cells include: 1) DNA/genomes, 2) specific protein/enzyme binding/functioning, 3) signal transduction and cancer genes, 4) apoptosis, and 5) ODC/polyamines/casein kinase II/myc oncoprotein.

DNA/Genomes

Numerous studies have illustrated that the multi-cationic polyamines react directly with the multi-anionic polyphosphorylated DNA molecules in cell free systems (43-46). SPD and SPM caused DNA to condense, to aggregate, to induce B-to-Z and B-to-A transitions, and to bend or contort the normal alpha helical structure. Some studies support the theory that polyamine binding to chromatin DNA may cause an increased or decreased availablity of genomic sites for DNA or RNA synthetases, and hence altered DNA and RNA synthesis. Polyamine depleted chromation was much more susceptible to DNAse digestion. While certain polyamine analogues (e.g., sym-norspermine) bound to chromatin DNA completely protected that DNA from DNAse digestion, it remains to be determined whether the polyamine induced modifications can result in changes in specific genomic functioning, or in only general genomic availabilities.

Specific protein/enzyme binding/functioning

Polyamines bind to many proteins. Most such bindings have been determined to be non-specific. Even the specific bindings to proteins (including enzymes) have not always resulted in any change in the activity/function of that polyamine bound protein. So, over the years, numerous polyamine bound proteins/enzymes have been reported, but the data has "not survived the tests of time". I will focus on "established" polyamine-protein interactions.

Elevated intracellular polyamine levels correlated with alterations in histone acetylation and deacetylation in normal and cancer cells (47-52). During cellular embryogenesis, differentiation, and oncogenesis, genes appear to be "turned off" and "turned on" by the acetylation-deacetylation of their associated histones. There are two classes of histone acetylases and histone deacetylases that can add or remove acetyl groups from the lysine resides of all types of histones. In general, acetylation of histones destablizes nucleosomes and allows for greater access to the DNA for transcription factors (more genes are functional). While deacetylation of histones stablizes nucleosomes and allowes decreased access to DNA for transcription factors (fewer genes were functional). Many histone acetylases and deacetylases can be regulated by gene promotors and gene inhibitors, which, in turn, may be controlled by various polyamines. These systems are modified in cells depleted of polyamines, in quiescent cells upon initation of cell proliferation, and in cancer cells when compared to their non-malignant counterparts.

Several protein kinases have been identified as enzymes that may be regulated by polyamines: polyamine dependent protein kinase (53), nuclear protein kinase NII (54), mammary gland polyamine responsive protein kinase (55), self phosphorylating polyamine stimulated protein kinase (56), and casein kinase II (CKII) (57-59). From this above list of protein kinases, only CKII has been purified from several mammalian tissues by using polyamine affinity chromotography. It has been studied with polyamine synthesis inhibitor drugs, polyamine catabolism stimulator drugs, and a variety of polyamine derivatives. CKII was stimulated by SPD, SPM, and several different molecular weight sizes of polylysines and polyornithines (maximal activation occurred with 8-10 amino groups), but was not stimulated with DFMO, MGBG, or polyarginines. Several polyamine derivatives (including BESpm and BE-4-4-4-4) prevented or reversed the SPM and polylysine activation of CKII. CKII phosphorylated more than 50 protein substrates including the myc oncoprotein (60-65).

Signal Transduction and Cancer Genes

Using various combinations of polyamine biosynthetic pathway inhibitors and stimulators, molecular linkages of polyamines to signal transduction and oncogene/cancer suppressor gene expressions in various cell types have been reported. Recent studies have suggested polyamines have linkages to the actions of epithelial growth factor (EGF), transforming growth factor beta (TGFβ), tumor necrosis factor alpha (TNFα), and hepatocyte growth factor (HGF) (66-71).

In addition, polyamine linkages have also been established for several oncogenes including: NF-Kappa B, c-myc, c-jun, and c-fos (68,72-77); and cancer suppressor genes including p53, Rb, $p21^{WAF1/CIP1/SDI1}$, and $p27^{Kip1}$ (78-80). Because the myc oncoprotein and the protein products of the above cancer suppressor genes are directly involved with the cell cycle and apoptosis, polyamines may be linked to key mechanisms involving mammalian cell proliferation, differentiation, and apoptosis. The above listed cancer genes are currently being studied, without and with components of the polyamine system, in cancer cells in culture, in animals, and from human tissue specimens (66-82).

Apoptosis

Recent studies indicate molecular linkages between polyamines and apoptosis (81-85). There are several established mechanistic triggers for cellular apoptosis (86). However, most of the current polyamine research focuses upon the cytochrome c pathway. Increases in the polyamine pathway in mammalian cells correlated with decreased mitochondrial membrane potential. This resulted in the release of mitochondrial cytochrome c, which stimulated a caspase 8 cascade activation down to caspase 3. Activation of caspase 3, in turn, is considered to activate the key endonucleases and proteases that directly cause apoptosis. The polyamines are postulated to affect mitochondrial transmembrane potential via increased activity of PAO and/or increased intracellular levels of PUT and/or H2O2 (catabolic pathway products) (84-85).

Casein Kinase II/myc oncoprotein/ODC/Polyamines

CKII activity was increased several fold in most types of cancer cells, and it was induced in many cell types upon cellular treatment with various growth factors (e.g., EGF) (63-67). The enzyme was also directly activated by SPD and SPM (see previous secton). CKII (and two other protein kinases) activated myc oncoprotein (which is a nuclear transcription factor) by phosphorylation of several serine residues in the nuclear entry, dimerization, DNA binding, and transactivation domains. In addition, in many major human cancer cells and tissues, the myc

oncogene is amplified several fold. Hence, the myc oncoprotein may be increased by both transcriptional and translational means in cancer cells. The myc oncoprotein induced >100 genomes and repressed >25 genomes. Several myc induced and repressed genomes are given in Table 2 (77,87-91).

The ODC/polyamines/CKII/myc oncoprotein linkages are directly involved in cell cycle control (77,87-93). One such example follows. Fast growing normal and cancer cells have elevated levels of ODC, polyamines, and CKII. And many cancer cells have amplified myc oncogene/oncoprotein. Phosphorylated myc oncoprotein could then be increased via transcription and translation control mechanisms, which, in turn, would induce the genes for cyclins A, D, and E, cyclin dependent kinase 2, cdc 25A and cdc 25B phosphateses, and ODC. Phosphorylated myc oncoprotein also repressed the cyclin dependent kinase inhibitor gene $p27^{Kip1}$. In addition, it has been observed that stimulation of arrested cells decreased another cyclin dependent kinase inhibitor gene $p21^{WAF1/CIP1/SDI}$ and increased phosphorylation of Rb. Increased cyclins and/or inhibition of cyclin dependent kinase inhibitors result in increased phosphorylation of Rb. This allows release of the Rb bound E2F transcription factor such that the E2F can positively tranduce genes directly involved in allowing passage through the G1-S cell cycle restriction point. Once a cell enters S phase, it will continue through M to produce two new daughter cells. In addition, myc oncoprotein induced dead box helicase, RNA polymerase I, carbamoyl P synthetase, eIF-4E and eIF-2α (all are critical to the synthesis of DNA and proteins in the S phase). These above described linkages suggest tight regulation and a continuum at the G1-S checkpoint in the cell cycle by polyamines. In addition, these linkages suggest that ODC to polyamines to CKII to phosphorylated myc oncoprotein to ODC to ..... linkages could feed forward-stimulate cell proliferation mechanisms.

The ODC/polyamines/CKII/myc oncoprotein linkages are also directly involved in apoptosis (81,86,91,94-98). As suggested earlier, the polyamine catabolic system enzyme, PAO, may be increased in some cancer cells, which could allow for increased intracellular levels of H2O2. The oxidation system of H2O2 could initate a decreased mitochondrial membrane potential and lead to cytochrome c induced apoptosis. In addition, myc oncoprotein induction of the bax gene would increase the bax protein in cells with amphlified myc. Bax protein can enter the mitochondrial membrane and cause cytochrome c leakages from the mitochondira, which in turn, can stimulate the cytochrome c to APAF to caspase 9 to caspase 3 pathway of apoptosis (81,86,97). However, when cancer cells, with and without amplified myc, are studied using a polyamine inhibitor (DFMO), four observations were made: 1) amplified myc induced rapid cell proliferation without causing apoptosis, 2) amplified myc induced rapid cell proliferation and apoptosis together, 3) apoptosis can occur without amplified myc,

Table 2. Genomes Controlled by Myc Oncoprotein

Induced Genes	Function of Protein Product
- cyclins A, D, E	- activate cyclin dependent kinases in cell cycle
- cyclin dependent kinase 2	- phosphorylates Rp protein in cell cycle
- cdc 25A and B phosphatase	- dephosphorylate and activate cyclin dep kinase 2
- FADD and caspase 8	- stimulate the apoptosis pathway
- bax	- stimulates the apoptosis pathway
- dead box helicase	- DNA synthesis
- RNA polymerase I	- RNA synthesis
- carbamoyl P synthetase	- synthesis of nucleic acids
- eIF-4E and 2α	- translation factors
- ornithine decarboxylase	- the rate limiting enzyme in polyamine synthesis
Repressed Genes	**Function of Protein Product**
- $p27^{Kip-1}$	- cyclin dependent kinase inhibitor in cell cycle
- Growth Arrest and DNA	- upon cell damage, inhibits cell proliferation
Damages (GADDs)	
- Growth Arrest Specific (GASs)	- inhibitor of cell proliferation

4) polyamines are involved in both cell proliferation and apoptosis in cancer cells (81,86,94-97). Obviously we do not yet understand all of the possible linkages, or maybe it is that different types of cancer cells have different apoptotic programs. At this point it should be noted that all cancer cells have been observed to have alterations in their cell cycle and/or apoptosis control systems (86,92)

Human Cancer Therapies

It has been established that high levels of intracellular polyamines correlate with high grades/stages of many human cancers. From these measurements direct correlations of increased metastatic potential of the cancers and increased negative prognosis for the patients have been established (99-102).

Several polyamine biosynthetic pathway drugs and polyamine analogues are currently being tested in human cancer patients. They are being evaluated individually, collectively, and in combination with other anti-cancer drugs. Because DFMO is relatively non-toxic, it is currently being used in many drug combinations and in cancer prevention (see below) trials. Current studies include PUT, DFMO, MGBG, BIS, DENSpm, BE-4-4-4-4, BE-3-7-3, BE-4-4-3, BE-4-4-4, BE-3-4-3, interferon, cps-platinum, indol-3 carbinol, topoisomerase inhibitors, HSV-1 thymidine kinase/ganciclovir (gene therapy), and 1-2-diaziridinyl-4,9-diazadodecane (radiotherapy) (31-40,81-82,103-110).

Human Cancer Prevention

Many polyamine studies now focus upon reduction of total body polyamines for cancer prevention, or reduction of total body organ polyamines (e.g., colon) for organ cancer prevention. Decreased intracellular levels of polyamines caused a decrease in oncogenesis by most organic toxic chemicals when carcinogenesis studies were performed in tissue culture, intact animal, or human studies. Therefore, prevention of human skin, stomach, colorectal, lung, prostate, and breast cancers studies are in progress using DFMO and other polyamine related drugs (39-42,111-121).

In General Summary, it would appear that the great expectations of 50 years ago that cancer could be controlled by controlling the intracellular level of polyamines has not yet fully materialized. There are at least two general reasons for this. It has become extremely difficult to deplete 100% of the polyamines from cancer tissue when that cancer tissue can obtain polyamines from the surrounding normal tissues. And we do not yet understand just how the polyamines control the intracellular mechanisms for cancer proliferation. Certainly, polyamine control focuses upon linkages in the events of the cell cycle and apoptosis. When these intracellular control systems are more completely understood, then a combination of drugs to deplete cancer cells of polyamines and additional drugs to interfer with the 'downstream' polyamine regulatory events will allow for more successful cancer therapy. However, we do know that decreasing intracellular levels of polyamines in normal tissues interfers with the oncogenesis mechanisms of toxic chemical carcinogens. Therefore, today, chemoprevention of cancers, using anti-polyamine drugs, can be utilized for high risk population groups in attempts to decrease their cancer risk.

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