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Archaeal Digoxin and Oncogenesis

Introduction

Changes involving the isoprenoid pathway have been described in neoplasms. The isoprenoid pathway produces key four metabolites important in cellular function - digoxin (an endogenous Na^+-K^+ ATPase inhibition), dolichol (important in N-glycosylation of proteins). ubiquinone (a component of the mitochondrial electron transport chain and membrane antioxidant) and cholesterol.

Alteration in membrane Na^+-K^+ ATPase has been described in oncogenesis suggesting a possible role for endogenous digoxin. An important feature of malignant transformation is loss of the cholesterol feedback inhibition mechanism that regulates cholesterol synthesis. Cancer cells seem to require an increase in the concentration of cholesterol and cholesterol precursors. Prevention of tumour-cell growth can be achieved by restricting either cholesterol availability or cholesterol synthesis. In vivo-and-cell-culture experiments have shown that lowering the plasma cholesterol concentration or intervening in the mevalonate pathway with HMG CoA reductase inhibitors decreases tumour growth. Another key protein in the internal signalling pathway that triggers cell growth is ras. ras is activated by hooking a 15 carbon farnesyl chain to ras by the enzyme farnesyl transferase. Farnesyl transferase inhibitors are used to block K-ras-driven tumours.

Digoxin by its inhibition of Na^+-K^+ ATPase can alter intracellular calcium / magnesium ratios in the cell leading to free radical generation. Alteration in ubiquinone which is a component of the mitochondrial electron transport chain and a membrane antioxidant, can also lead to mitochondrial dysfunction and free radical generation. Defects in structure and function of mitochondria have been described in neoplasms. Free radical mechanisms have been implicated in tumourogenesis. Free radicals are required for the action of the oncogene coded growth factors. Digoxin induced membrane Na^+-K^+ ATPase inhibition can

produce magnesium depletion leading to altered glycoconjugate metabolism. Altered glycoproteins and dolichol have been described in neoplasms. The dolichol pathway is important in N-glycosylation of protein. Altered glycosylation of serum transferrin has been reported in neoplastic lesions. Abnormal glycoconjugates have been described in neoplastic disorders. A number of fucose and sialic acids containing carbohydrate ligands are important in malignant cell transformation. Glycosylation inhibitors are used to treat neoplasms. In some tumours, interaction of tumour and host cells with adhesion and extracellular matrix molecules like heparan sulphate, proteoglycan and syndecan are important.

Digoxin has been reported to regulate the transport of amino acids, especially the neutral amino acids. Tryptophan metabolism has also been implicated in neoplastic disorders and immune activation. Interferons act by inducing the enzyme indoleamine 2,3-dioxygenase which catalyses the catabolism of tryptophan along the kynurenine pathway. This leads to tryptophan depletion and increase in the level of its metabolites kynurenine and quinolinic acid. Cachexia related to cancer has also been related to indoleamine 2,3-digoxygenase induction and depletion of tryptophan by enhancing its catabolism. The kynurenine pathway can also contribute to oncogenesis. Neurotransmitters could contribute to the regulation of the immune response. Elevated serotonin and reduced dopamine levels have been related to immune activation and immunoproliferation. Tryptophan and tyrosine catabolism could be important in this respect with regard to non-Hodgkin's lymphoma.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the

enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related cancer.

This study was undertaken to assess the following parameters in Non-Hodgkin's Lymphoma (NHL) and CNS astrocytomas: (1) The isoprenoid pathway, (2) The tryptophan/tyrosine catabolic patterns, (3) Glycoconjugate metabolism, and (4) RBC membrane changes as a reflection of neoplastic cell membrane change (the isoprenoid pathway produces four metabolites which can regulate membrane function and structure-dolichol, digoxin, cholesterol and ubiquinone). A hypothesis implicating membrane Na^+-K^+ ATPase inhibition as pivotal to all these changes is also presented.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were increased in CNS astrocytmas and NHL when compared with controls. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma while that of tyrosine, dopamine and noradrenaline was decreased in CNS astrocytomas and NHL.

(3) Nicotine could be detected in the plasma of patients with CNS astrocytomas and NHL but was not detectable in control serum. Morphine and strychnine was not detected in the plasma of these patients.

(4) The concentration of total glycosaminoglycans (GAG) increased in the serum of CNS astrocytomas and NHL patients. The concentration of heparan sulphate (HS) heparin (H), chondroitin sulphates (ChS) and hyaluronic acid was increased in NHL and CNS astrocytomas, while that of dermatan sulphate (OS) was decreased in CNS astrocytomas and increased in NHL. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in these patients. The concentration of gangliosides, glycosyl-diglycerides, cerebroside and sulphatide showed significant increase in the serum of these patients.

(5) The activity of glycosaminoglycan (GAG) degrading enzymes - beta glucuronidase, beta N-acetyl hexoseaminidase, hyaluronidase and cathepsin-D - was increased in CNS astrocytomas and NHL when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase increased in CNS astrocytomas and NHL patients.

(6) The concentration of total GAG and hexose and fucose residues of glycoproteins in the RBC membrane decreased significantly in CNS astrocytomas and NHL. The concentration of RBC membrane cholesterol was unaltered in CNS astrocytomas and NHL while that of phospholipid decreased. The ratio of RBC membrane cholesterol: phospholipids increased in CNS astrocytomas and NHL.

(7) Concentration of total serum cholesterol and LDL cholesterol was not significantly altered while HDL cholesterol showed a significant decrease in the plasma in CNS astrocytomas and NHL. Serum triglycerides and free fatty acids (FFA) increased in CNS astrocytomas and NHL.

(8) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in CNS astrocytomas and NHL. The concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of glutathione was decreased and of alpha tocopherol was unaltered in CNS astrocytomas and NHL. Iron binding capacity and ceruloplasmin decreased significantly in CNS astrocytomas and NHL while albumin was reduced.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Oncogenesis

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase can decrease this enzyme activity. In CNS astrocytomas and NHL there was significant inhibition of the RBC membrane Na^+-K^+ ATPase. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. The decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low

magnesium can cause further inhibition of Na^+-K^+ ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of CNS astrocytomas and NHL. Serum magnesium was assessed in CNS astrocytomas and NHL and was found to be reduced. Increased intracellular calcium activates phospholipase C beta which results in increased production of diacyglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular proliferation. The decreased intracellular magnesium can produce dysfunction of GTPase activity of the alpha - subunit of G-protein. This results in ras oncogene activation, as more of the ras is bound to GTP rather than GDP. Phosphorylation mechanisms are required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect. Intracellular magnesium depletion can produce defective phosphorylation of microtubule associated proteins (MAP) resulting in microtubule related spindle fibre dysfunction and chromosomal non-dysjunction. This produces the characteristic neoplastic cellular polyploidy and aneuploidy. Upregulation of the isoprenoid pathway can result in increased production of farnesyl phosphate which can farnesylate the ras oncogene producing its activation.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Oncogenesis

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also

reported to influence the transport of various metabolite across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important - tryptophan, a precursor for nicotine and strychnine and tyrosine a precursor for morphine. We have a already shown the presence of endogenous nicotine and strychnine in the brain of rats loaded with tryptophan and morphine in the brain of rats loaded with tyrosine. The results now obtained show that the concentration of tryptophan, quinolinic acid and serotonin was higher in the plasma of patients with CNS astrocytomas and NHL while that of tyrosine, dopamine and norepinephrine was lower. Serum of patients with CNS astrocytomas and NHL showed the presence of high amounts of nicotine in their serum. Morphine and strychnine were absent in the serum of these patients. Thus there is increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the patient's serum. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in all the disorders studied could be due to the fact that the hyperpolarising neurotransmitters (dopamine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, nicotine and quinolinic acid) are increased.

The neurotransmitter pattern of reduced dopamine and noradrenaline, and increased serotonin can contribute to cancer related psychosis. This neurotransmitter pattern is common to neoplasms (CNS astrocytomas and NHL) and schizophrenia (paper under publication). A schizoid state of mind can predispose the patients to the development of neoplasms. Alteration in natural killer cell activity has been reported in psychiatric disorders. Serotonin and acetyl choline promote cell proliferation and dedifferentiation by inhibiting denyl cyclase or by activating phospholipase-C (PLC). Nicotine by binding to the nicotinic receptor promotes cholinergic transmission. Dopamine and

noradrenaline elevate cyclic AMP levels and inhibit cell proliferation and differentiation. Increased quinolinic acid can lead to cancer related cachexia. Serotonin dopamine and noradrenaline receptors have been demonstrated is increased with the corresponding reduction in dopamine and noradrenaline in the brainstem monoaminergic nuclei. Thus elevated serotonin and reduced noradrenaline and dopamine can contribute to the immune activation and immunoproliferation in non-Hodgkin's lymphoma. Decreased morphine levels can lead to the increased metastatic property of tumours as morphine has a suppressing effect on tumour metastasis and tumour growth.

In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^+-K^+ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^+-K^+ ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid and serotonin can also contribute to NMDA excitotoxicity. Quinolinic acid and serotonin are positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in cellular proliferation. Excitatory amino acids like glutamate can act as trophic factors and promote cellular proliferations.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Oncogenesis

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^+-K^+ ATPase related Magnesium depletion can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead to defective metabolism of sphinganine, producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In Magnesium deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results now obtained show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbophydrate components of glycoproteins (hexose, fucose and sialic acid) in CNS astrocytomas and NHL. The increase in the carbohydrate components - total hexose, fucose and sialic acid - in CNS astrocytomas and NHL was not to the same extent suggesting qualitative change in glycoprotein structure. The pattern of change in individual GAG was that HA, H, HS, ChS and DS (except in CNS astrocytomas where DS was reduced) increased in the serum in CNS astrocytomas and NHL. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum in CNS astrocytomas and NHL. Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced

lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered calcium/magnesium ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

The protein processing defect can result in defective glycosylation of endogenous tumour antigens and exogenous viral glycoprotein antigens with consequent defective formation of the MHC-antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. There is dysfunction of this in the presence of magnesium deficiency. This results in defective transport of MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD_4/CD_8 cell/NK cell. Defective presentation of exogenous viral antigens can produce immune evasion by the virus leading to viral persistence and oncogenesis consequent to viral oncogenesis. This is especially true in the case of Non-Hodgkin's lymphoma (both T-cell and B-cell type) where the ebstein barr virus has been linked to the pathogenesis. Defective presentation of endogenous tumour antigens can lead on to loss of NK cell (natural killer cell) immunosurveillance and oncogenesis. Altered cell surface glycoproteins, glycolipids and Gag can lead to defective contact inhibition and oncogenesis. A number of fucose and sialic acids containing natural ligands have been implicated in neoplastic transformation and metastasis as also immune activation and lymphocytic proliferation.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Oncogenesis

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The RBC membrane cholesterol was unchanged while the phospholipids were reduced resulting in an increased cholesterol phospholipid ratio. The concentration of total GAG, hexose and fucose residues of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. Similar changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading

enzymes into the serum. Defective peoxisomal membranes lead to catalase dysfunction which has been documented in CNS astrocytomas and NHL.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Oncogenesis

The archaeaon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeaon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in most of the cases which may be the result of low tyrosine levels, reported in CNS astrocytomas and NHL consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone, which is important and contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore causing a collapse of the hydrogen gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular magnesium deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^+-K^+ ATPase triggering the cycle of free radical generation

again. The free radicals and scavenging enzymes were estimated in all these disorders. There was increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone and reduced glutathione in CNS astrocytoma and NHL. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in CNS astrocytoma and NHL suggesting reduced free radical scavenging. Alpha tocopherol values were unchanged in both neoplasms. In our study the iron binding capacity and serum ceruloplasmin are reduced suggesting increased amounts of free iron and copper, promoting free radical generation. Ceruloplasmin is a 132 KD monomeric copper oxidase which has been implicated in iron metabolism because of its catalytic oxidation of Fe^{2+} to Fe^{3+} (feroxidase activity). In the presence of iron in Fe^{2+} form, the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intra cellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. The peroxisomal membrane is defective owing to the membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The low intracellular magnesium consequent to Na^+-K^+ ATPase inhibition and the resulting low ATP can result in decreased synthesis of glutathione. Glutathione peroxidase, a selenium

containing enzyme oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs Na^+-K^+ ATPase inhibition leads to decreased formation of glucose-6-phosphate and down regulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus the glutathione system of free radical scavenging is defective in the presence of membrane Na^+-K^+ ATPase inhibition. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. Opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and a decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the oncogenesis. Free radicals are required for the action of growth factors and promote cellular proliferation.

The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also lead to volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases cytochrome C into the cytoplasm. This results in activation of caspase-3. Caspase-3 activation can cleave and inactivate P_{21} involved in linking DNA duplication to cell division resulting in a polyploidal cell and oncogenesis.

Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation in Relation to Oncogenesis - Relation to Immune Activation

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-3, 4, 5, 6 and TNF alpha. This can explain the immune activation in Non-Hodgkin's lymphoma and paraneoplastic syndromes. Membrane Na^{+}-K^{+} ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium. Defective presentation of glycoprotein neuronal antigens to the CD_4 and CD_8 cell can explain the immune dysregulation and autoimmunity describe in paraneoplastic syndromes.

Thus the defective isoprenoid pathway can promote oncogenesis by the following mechanisms, (1) Altered calcium/magnesium ratios promoting ras oncogene activation and defective function of the P_{53} tumour suppressor gene, (2) Protein processing defect and defective presentation of tumour antigens and defective immunosurveillance. This can also lead to defective contact inhibition. Defective processing of viral glycoprotein antigens and their presentation can lead to viral persistence and oncogenesis, (3) Mitochondrial defect and free radical generation. This also leads to caspase-3 activation and cleaving of P_{21} protein which couples cell division to DNA duplication, (4) Intracellular magnesium depletion can produce defective phosphorylation of MAP (microtubule associated proteins) resulting in microtubule related spindle fibre dysfunction and cellular polyploidy and aneuploidy, (5) Digoxin related tryptophan/tyrosine transport defect leading to increase in neurotransmitters that

promote cell proliferation (nicotine and serotonin) and decrease in neurotransmitters that inhibits cell proliferation (dopamine and noradrenaline). This also leads to quinolinic acid related cachexia and immunoproliferation, and (6) Increased production of famesyl phosphate leading to farnesylation of ras oncogene and its activation.

References

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