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A REVIEW ARTICLE ON ANTICANCER AGENTS AND USE OF STATINS AS POTENTIAL ANTICANCER DRUG

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ABSTRACT

Statins have been shown to inhibit cell proliferation in vitro and tumor growth in animal models. Various studies have also shown a decreased cancer-specific mortality rate in patients who were prescribed these medications. Statins inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme of the mevalonate pathway. Statins induce tumour-specific apoptosis through mitochondrial apoptotic signaling pathways, which are activated by the suppression of mevalonate or geranylgeranyl pyrophosphate (GGPP) biosynthesis. The statins inhibit the production of endogenous cholesterol and may influence also cell proliferation and migration. A reduction on the cholesterol level could lead to decreased proliferation and metastasis of cancer cells. Statins had anticancer proprieties (halting cell- cycle progression in cancer cells) and reduced the risk of cancer recurrence. Many of cholesterol products resulting of synthesis pathway are used in cells proliferation. Disruption of these processes conduct to inhibition of cancer growth and metastasis, reduce angiogenesis and stimulate apoptosis. Currently, there are many ongoing clinical trials aimed at exploring the potential of statins to lower the mortality and the disease-recurrence risk. All these results are the foundation of new treatment directions in cancer therapy.

INTRODUCTION

The global burden due to cancer increased to 14.1 million new cases and 8.2 million cancer-associated mortalities in 2012. Statistics published in September 2018 by the World Health Organization revealed that cancer is responsible for one in six deaths worldwide. The most diagnosed and deadly types of cancer are lung cancer (LC), breast cancer (BC), colorectal cancer (CRC) and prostate cancer (PC). The most common risk factors responsible for cancer occurrence include smoking, obesity, unhealthy diet, alcohol consumption and viral infections. Cancer, which is represented by a large number of conditions, is defined as an uncontrolled proliferation of cells that possess metastatic properties. These cells are characterized by changes in their activity, such as the suppression of apoptotic mechanisms, the disruption of cell adhesion and signaling, and changes that occur as a result of genetic mutations. Chemotherapy is a common approach to cancer management, which is currently used in a curative, palliative, or adjuvant capacity. Several classes of chemotherapeutic medications have been used clinically, including DNA alkylating agents, platinating agents, and antimetabolites. Many current chemotherapeutics have been shown to kill tumour cells by inducing apoptosis.[1]

Antimetabolites which are incorporated into RNA or act to inhibit protein synthesis have not proved to be used in cancer treatment. Certain antimetabolites inhibit the biosynthesis of the nucleic acids. Interruption in the formation of these essential components of DNA and RNA, which each cell produces in order to function and multiply, results in cell death.[2] Unphysiological doses of exogenously administered steroid hormones alter hormonal balance in the patient and modify the growth of some cancers arising from tissues particularly susceptible to hormonal influences. The mechanism whereby the steroid hormones stimulate or inhibit cellular growth and function is not clear, but it is believed to be at the level of processes concerned with RNA to protein synthesis. The vinca alkaloids, vincristine and vinblastine, disorganize the mitotic spindle to arrest cell division. Vincristine is more effective in acute leukemia and vinblastine in Hodgkin's disease than the other plant alkaloids, colchicine and its derivatives and podophyllotoxin, which also produce metaphase arrest.[3] L-asparaginase acts in a unique manner to hydrolyse asparagine to aspartic acid, and neoplastic cells un able to make this amino acid, die if the supply of L-asparagine inthe circulat ing blood, on which they are dependent, is destroyed by the enzyme. Normal cells synthesize L-asparagine for their needs, and thus appear to be unaffected by the L-asparagine deficiency in the blood stream.[4]

Cell proliferation, differentiation and apoptosis

The rate of cell proliferation within any population of cells depends on three parameters: (*a*) the rate of cell division (Tc), (*b*) the fraction of cells within the population undergoing cell division (growth fraction), and (*c*) the rate of cell loss from the population due to terminal differentiation or cell death. The cell division cycle can be divided into two functional phases, S and M phases, and two preparatory phases, G1 and G2.

Normal tissues exhibit a regulated balance between cell proliferation and cell death. Programed cell death is an important component in the processes of normal embryogenesis and organ development. A distinctive type of programed cell death is called apoptosis.[5] Apoptosis can be triggered in mature cells by external stimuli such as steroids and radiation exposure. Studies of cancer cells have shown that both uncontrolled cell proliferation and failure to undergo programed cell death can contribute to neoplasia and insensitivity to anticancer treatments.[6]

Oncogenes

The first oncogenes were discovered through the study of retroviruses, RNA tumor viruses whose genomes are reverse-transcribed into DNA in infected animal cells. During the course of infection, retroviral DNA is inserted into the chromosomes of host cells. The integrated retroviral DNA, called the provirus, replicates along with the cellular DNA of the host. Retroviral oncogenes are altered versions of host cellular proto-oncogenes that have been incorporated into the retroviral genome by recombination with host DNA, a process known as retroviral transduction.[7]

Mechanism of oncogenes activation

The activation of oncogenes involves genetic changes to cellular proto-oncogenes. The consequence of these genetic alterations is to confer a growth advantage to the cell[8]. Three genetic mechanisms activate oncogenes in human neoplasms: (*i*) mutation, (*ii*) gene amplification, and (*iii*) chromosome re-arrangements.

Mutation

Mutations activate proto-oncogenes through structural alterations in their encoded proteins. These alterations, which usually involve critical protein regulatory regions, often lead to the uncontrolled, continuous activity of the mutated

protein. In human tumors, however, most characterized oncogene mutations are base substitutions (point mutations) that change a single amino acid within the protein.

Gene amplification

Gene amplification refers to the expansion in copy number of a gene within the genome of a cell. Gene amplification was first discovered as a mechanism by which some tumor cell lines can acquire resistance to growth-inhibiting drugs. The process of gene amplification occurs through redundant replication of genomic DNA, often giving rise to karyotypic abnormalities called double-minute chromosomes (DMs) and homogeneous staining regions. Both DMs and HSRs represent large regions of amplified genomic DNA containing up to several hundred copies of a gene. Amplification leads to the increased expression of genes, which in turn can confer a selective advantage for cell growth.

Chromosomal rearrangements

Recurring chromosomal re-arrangements are often detected in hematologic malignancies as well as in some solid tumors. These re-arrangements consist mainly of chromosomal translocations and, less frequently, chromosomal inversions. Chromosomal re-arrangements can lead to hematologic malignancy by two different mechanisms: (i) the transcriptional activation of proto-oncogenes or (ii) the creation of fusion genes. Transcriptional activation, sometimes referred to as gene activation, results from chromosomal re-arrangements that move a proto-oncogene close to an immunoglobulin or T-cell receptor gene. Transcription of the proto-oncogene then falls under control of regulatory elements from the immunoglobulin or T-cell receptor locus. This circumstance causes deregulation of proto-oncogene expression, which can then lead to neoplastic transformation of the cell.[9]

GROWTH FACTOR SIGNAL TRANSDUCTION IN CANCER

Growth factors

Some viral oncogenes are altered versions of normal growth factor receptors that possess intrinsic tyrosine kinase activity. Receptor tyrosine kinases, as these growth factor receptors are collectively known, have a characteristic protein structure consisting of three principal domains: (i) the extracellular ligand-binding domain, (ii) the transmembrane domain, and (iii) the intracellular tyrosine kinase catalytic domain. The binding of a growth factor to the extracellular ligand-binding domain of the receptor results in the activation of the intracellular tyrosine kinase catalytic domain.[10] The recruitment and phosphorylation of specific cytoplasmic proteins by the activated receptor then trigger a series of biochemical events generally leading to cell division. Because of the role of growth factor receptors in the regulation of normal cell growth, it is not surprising that these receptors constitute an important class of proto-oncogenes.[11]

Signal transducers

Mitogenic signals are transmitted from growth factor receptors on the cell surface to the cell nucleus through a series of complex interlocking pathways collectively referred to as the signal transduction cascade. Many proto-oncogenes are members of signal transduction pathways. These consist of two main groups: nonreceptor protein kinases and guanosine triphosphate (GTP)-binding proteins.

Historical aspect of cancer

In the 1920s, Warburg studied glycolysis in a wide variety of human and animal tumors and found that there was a general trend toward an increased rate of glycolysis in tumor cells. He noted that when normal tissue slices were incubated in a nutrient medium containing glucose, but without oxygen, there was a high rate of lactic acid production (anaerobic glycolysis); however, if they were incubated with oxygen, lactic acid production virtually stopped. The rate of lactic acid production was higher in tumor tissue slices in the absence of oxygen than in normal tissues, and the presence of oxygen slowed, but did not eliminate, lactic acid formation in the tumor slices. Warburg concluded that cancer cells have an irreversible injury to their respiratory mechanism, which increases the rate of lactic acid production even in the presence of oxygen. He regarded the persistence of this type of glycolysis as the crucial biochemical lesion in neoplastic transformation. This old idea still has some credence in that there are hypoxic areas in the core of tumors, where anaerobic metabolism predominates. This has clinical implications because hypoxic cells do not respond as well to certain anticancer drugs and radiation therapy.

In the early 1950s, Greenstein formulated the "convergence hypothesis" of cancer, which states that the enzymatic activity of malignant neoplasms tends to converge to a common pattern. Although he recognized some exceptions to this rule, he considered the generalization, based mostly on repeatedly transplanted tumor models, to be valid. It is now more fully appreciated that even though cancer cells do have some commonly increased metabolic pathways, such as those involved in nucleic acid synthesis, there is tremendous biochemical heterogeneity among malignant neoplasms, and that there are many fairly well-differentiated cancers that do not have the common enzymatic alterations he suggested. Thus, cancers do not have a universally uniform malignant phenotype as exemplified by their enzyme patterns. About 10 years later, Potter suggested that the proteins lost during carcinogenesis may be involved in the feedback control of enzyme systems required for cell division, and he proposed the "feedback deletion hypothesis". In this hypothesis, Potter postulated that "repressors" crucial to the regulation of genes involved in cell proliferation are lost or inactivated by the action of oncogenic agents on the cell, either by interacting with DNA to block repressor gene transcription or by reacting directly with repressor proteins and inactivating them.[12]

Genetic basis for cancer development

In 1866, Broca described a family in which many members developed breast or liver cancer, and he proposed that an inherited abnormality within the affected tissue allowed tumor development. Following the rediscovery of Mendel's work, studies of the rates of spontaneous mammary tumor formation among various inbred strains of mice led Haaland to argue that tumorigenesis could behave in a formal sense as a mendelian genetic trait. Similarly, Warthin's analysis of the pedigrees of cancer patients at the University of Michigan Hospital between 1895 and 1913 identified four multigenerational families with susceptibilities to specific cancer types that appeared to be transmitted as autosomal dominant mendelian traits. Although these and other studies suggested the existence of an inherited genetic basis for some cancers, other explanations for familial clustering were possible (e.g., shared exposure to a carcinogenic agent in the environment or diet).

MECHANISM OF ACTION OF STATINS

Statins have gained much attention for the prevention and treatment of cancer as they are capable to inhibit inflammation, angiogenesis, and proliferation and to induce apoptosis. The statins inhibit the production of endogenous

cholesterol and may influence also cell proliferation and migration. A reduction on the cholesterol level could lead to decreased proliferation and metastasis of cancer cells.

Cholesterol has also been shown to play multifaceted roles in tumorigenesis. statins have been shown to elicit their anticancer effects through the depletion of cholesterol. Cholesterol along with isoprenoid intermediates are synthesized through the mevalonate pathway. In this process, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) is converted into mevalonate via HMG-CoA reductase. Statins, due to their structural similarity to HMG-CoA, are competitive inhibitors of HMG-CoA reductase, and thereby have the ability to suppress cholesterol synthesis.[13]

Statins reduce the level of total cholesterol, LDL-C, VLDL-C, triglycerides, apo-B, and increase the level of HDL-C. Statins also have cardiovascular protective effects (pleiotropic effects), which are primarily because of the inhibition of production of prenylated proteins (mainly farnesyl pyrophosphate and geranylgeranyl pyrophosphate) in the cholesterol biosynthetic pathway. Statins are classified based on their intensity as follows:

- **Low-intensity statins:** These include 20 to 40 mg fluvastatin, 20 mg lovastatin, 1 mg pitavastatin, 10 to 20 mg pravastatin, or 10 mg simvastatin. Low-intensity statins reduce LDL-C by less than 30%.
- **Moderate-intensity statins:** These include 10 to 20 mg atorvastatin, 80 mg fluvastatin, 40 mg lovastatin, 2 to 4 mg pitavastatin, 40 to 80 mg pravastatin, 5 to 10 mg rosuvastatin, or 20 to 40 mg simvastatin. Moderate-intensity statins reduce LDL-C by 30 to 50%.
- **High-intensity statins:** These include 40 to 80 mg atorvastatin or 20 to 40 mg rosuvastatin. High-intensity statins reduce LDL-C by greater than 50%.

  Statins administration in specific patient population groups:
- Elderly patients: In individuals older than 75 years of age, who have a clinically significant ASCV, the recommendation is to start them on moderate-intensity statins rather than high-intensity statins; this is because of increased side effects associated high-intensity statins, and reduction in the efficacy of metabolic pathways in elderly individuals.
- Renal impairment: Atorvastatin, fluvastatin, pravastatin, or simvastatin are indicated in patients with chronic kidney disease since they do not undergo renal elimination, and hence, no dose adjustment is required.
- Liver impairment: Pravastatin and rosuvastatin can be used in patients with compensated liver disease since they are metabolized to a lesser extent by the liver in comparison to other statins. When initiating statins in patients with liver disease, patients must abstain from alcohol. The statins mentioned above should initiate at a low dose and liver enzymes, and LDL-C should get monitored within 1 to 3 months. If no significant change occurs in the level of aminotransferase, therapy does not achieve the LDL-C target, increase the dose of statins. Statins are contraindicated in patients with acute liver failure or decompensated cirrhosis.[13]

OVERVIEW OF VARIOUS STATIN DRUGS

In a previous study, comparing atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin, the latter one gave the best results regarding patients' survival. The antimyeloma activity of statins in humans was first reported with the concomitant simvastatin administration in refractory multiple myeloma (MM), which showed reduced drug resistance. One study demonstrated that simvastatin decreases the cholesterol content of lipid rafts in prostate cancer cells, which hinders AKT signaling and induces apoptosis.[14] Fluvastatin or atorvastatin as bone-targeting therapy affected certain bone biomarkers and provided bone response in several patients. However, no statistically significant

improvement in time to skeletal events was observed. The survival of pediatric brain stem tumor patients was significantly increased with metronomic treatment with carboplatin and vincristine associated with fluvastatin and thalidomide.

It was shown that liposomes co-loaded with simvastatin and doxorubicin targeted towards prostate cancer cells may lead to 80% inhibition of tumour growth in an in vivo model. It was also shown that simvastatin and doxorubicin may exert a synergistic, antiangiogenic effect.

Pravastatin combination significantly improved survival of patients with advanced hepatocellular carcinoma.[15]

Statins are among drugs that have been shown to possess apoptosis-inducing effects. They were originally developed as a treatment for hypercholesterolemia. The literature describes two main paths through which cholesterol contributes to cancer onset. The first one involves the fundamental role of cholesterol in processes such as cell adhesion and signaling, necessary for normal cell functioning, while the second one refers to its function as a precursor in the synthesis of sex hormones and other isoprenoid intermediates, responsible for the development of particular types of cancer.

The first statin, mevastatin, was identified and isolated by Endo (2004), being the first cholesterol-lowering drug. Today statins are classified into two groups: type-I derivatives are derived from fermentation products, such as mevastatin, lovastatin, pravastatin, and simvastatin. Type-II statins, including fluvastatin, atorvastatin, cerivastatin, pitavastatin, and rosuvastatin, are drugs of synthetic origin. Lovastatin and simvastatin are lactones, thus closed ring prodrugs, which are transformed into their active open forms in the body; other statins are administered orally as active, opened rings, forming hydroxyl acids. The two groups differ in their ability to inhibit HMGCR and in their lipophilicity. The pharmacological activity of statins is dictated by their different chemical structures, lipophilicity/hydrophilicity, kinetic profile, rate of metabolism, and the formation of active and inactive metabolites.

Drug interactions

- **Macrolide antibiotics:** clarithromycin and azithromycin
- **Immunosuppressants:** immunosuppressive agents, including cyclosporine, or tacrolimus, are CYP 3A4 inhibitors. Among the statins, pravastatin or fluvastatin are the recommended agents for use in combination with immunosuppressive agents.
- **Protease inhibitors:** protease inhibitors interact with statins and increase the risk of muscle toxicity. Fluvastatin or pravastatin is the statin of choice in patients taking protease inhibitor.

Monitoring

Monitor lipid profile, liver function tests, creatine kinase (CK) and thyroid function tests in individuals who start statin treatment:

- **Lipid profile:** Perform lipid profile at baseline before initiating statins. The lipid panel should be repeated two months after starting the therapy. If the level of LDL-C reduction is less than expected in an individual adherent to medication, then increase the dose of statin or change to another potent statin medication and repeat lipid profile after two months. If the level of LDL-C is within the expected range, repeat the lipid profile every 6 to 12 months.

- **Liver function tests:** Perform liver function tests at baseline before initiating statins. Routine monitoring of LFTs is not a recommendation. LFTs require rechecking when the patient develops symptoms of liver disease.
- **Creatine kinase (CK):** CK levels are optionally obtainable at baseline before initiating statins. Routine monitoring of CK is not a recommendation.
- **Thyroid function tests:** Hypothyroidism can cause abnormal lipid profile and myopathy. Recommendations are to obtain thyroid hormone levels before starting statin therapy.[16]

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