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IMMUNITY SYSTEM AGAINST BRAIN TUMOUR

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ABSTRACT

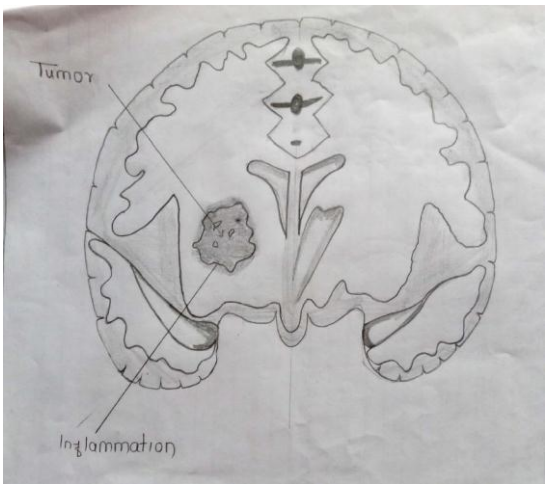
Cytokines are molecular messengers that allow the cells of the immune system to communicate with one another to generate a coordinated, robust, but self-limited response to a target antigen. The growing interest over the past two decades in harnessing the immune system to eradicate cancer has been accompanied by heightened efforts to characterize cytokines and exploit their vast signalling networks to develop cancer treatments. Cytokines directly stimulate immune effector cells and stromal cells at the tumour site and enhance tumour cell recognition by cytotoxic effector cells. Recent years have seen a number of cytokines, including GM-CSF, IL-7, IL-12, IL-15, IL-18 and IL-21, enter clinical trials for patients with advanced cancer. There is ongoing pre-clinical work supporting the neutralization of suppressive cytokines, such as IL-10 and TGF-β in promoting anti-tumour immunity. In addition, advances in adoptive cell therapy have relied on the use of cytokines to create an in vitro, highly controlled environment for the optimal development of anti-tumour T cells. Numerous animal tumour model studies have demonstrated that cytokines have broad anti-tumour activity and this has been translated into a number of cytokine-based approaches for cancer therapy. The review will also describe new cytokines in pre-clinical development, combinations of biological agents, novel delivery mechanisms, and potential directions for future investigation using cytokines.

KEYWORD: Cytokines directly stimulate immune effector cells and stromal cells at the tumour site and enhance tumour cell recognition by cytotoxic effector cells.

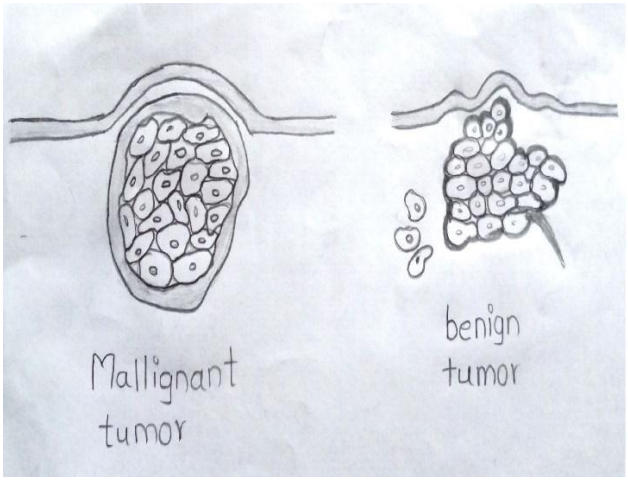
INTRODUCTION

Whatis a brain tumour?

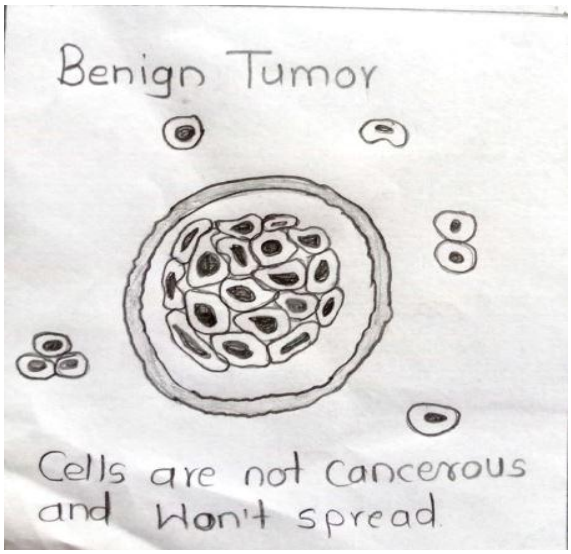
A brain tumour is a collection, or mass, of abnormal cells in the brain. A skull, which encloses the brain, is very rigid. Any growth inside such a restricted space can cause problems. Brain tumours can be cancerous (malignant) or noncancerous (benign).[1] When benign or malignant tumours grow, they can cause the pressure inside your skull to increase. This can cause brain damage, and it can be life-threatening.[1,2]

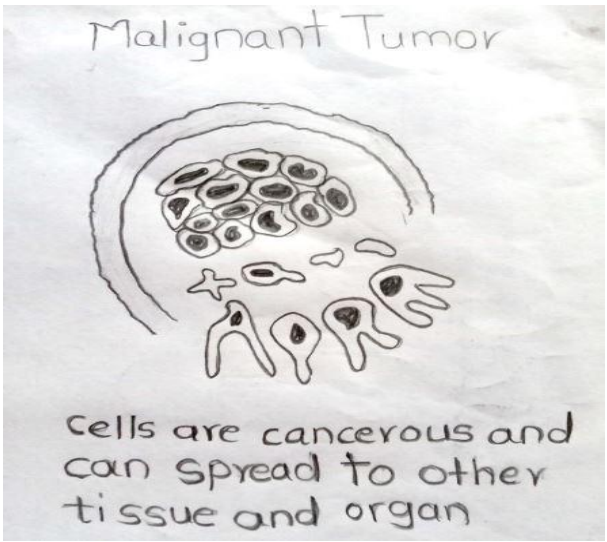


Malignant tumour



Benign tumour





Definition

A brain tumour is mass or growth of abnormal cells in the brain. OR The growth of abnormal cells in the tissue of the brain or skull. It can be benign (not cancer) or malignant (cancer).[2]

Benigntumour- This tumour is not cancer. It tends to grow slowly. The benign tumour does not grow into nearby tissue. If we remove, they do not grow back. It depends on size and location in brain.[1,2]

Malignanttumour- Malignant tumour is cancer. It is grow fast and grow into nearby tissue. This can make it hard to remove fully. It may be grow back after treatment.[1,2]

Cancerous tumours having two type: primary tumour and secondary tumour.

- **primarytumour** start with in the brain.
- **Secondarytumour** spread from elsewhere known as brain metastasis. In this tumour is from a cancer that start in anothIntroductioner part of body, then spreads to the brain.[4]

CAUSES OF BRAIN TUMOUR

The exact cause of a brain tumour is often unknown.It develops when its cells in the body divides and grow at an excessive rate. Typically the body is able to balance cell growth and division. When old or damage cell die, they are automatically replaced with new, healthy cell However, factors that can increases risk of brain cancer include exposure to high doses of ionizing radiation and family history of brain cancer**.**[1,5]

RISKFACTORS

1. Age –The brain tumour is more common in children and adults. Although people of any can develop brain tumour.

2. Gender- Mostly in the men are more likely than woman to produces brain tumour. Some special type of brain tumour, like meningioma, are more common in women.[6]

3. Homeandworkexposure- The exposure solvent, oil product, rubber, vinyl chloride may increases risk of producing brain tumour.[5,6]

4. Familyhistory- 5%of brain tumours may linked to hereditary genetic factors including Li-Fraumeni syndrome, neurofibromatosis, nevoid basal cell carcinoma syndrome, tuberous sclerosis, Turcot syndrome and Von-Hippel-Lindau disease.[6]

5. Exposuretoinfection, viruses, andallergens- Epstein-Barr virus (EBV) produces infection which increases risk of CNS lymphoma. EBV is commonly known as virus that cause mononucleosis or mono. In research the high level of virus called as cytomegalovirous (CMV). It also found or present in brain tissue. Other type of virus can show the causes of brain tumours in research on animals. The increases infection, other virus and allergens increases the brain tumour in people.[1,6]

6. Electromagnetic field – The evaluating of role of electromagnetic field, such as energy from power line and from cell phone uses, show no link of an increased risk of developing brain tumour in adults. Because conflicting information regarding risk in children.[7]

7. Race **and ethnicity**- The white people in United States are more developing gliomas but less developing meningioma in the black people. The people from northern Europe are more twice as likely to develop brain tumour as people in japan,[6]

8. Ionizing radiation- In brain or head treatment with ionizing radiation. It contain x-ray has been shown to be risk factor for brain tumours.

9. Head injury and seizures- serious head trauma has long studied for its relationship to brain tumour. A history of seizure has also been linked between bead trauma and meningioma, but because a brain tumour can cause seizure. It is not if seizure increase risk of brain tumour. If seizure occur because to from or if anti-seizure medication increase the risk.[7]

10. N-nitroso compound- the studies of diet and vitamin supplementation indicate the dietary N-nitroso compound raise risk of both children and adults brain tumour. Dietary N-nitroso compound are formed in the body from nitrites or nitrates found in cured meats, cigarette smoke, and cosmetics.[8]

SYMPTOMS

Headaches- which may be serve with activity or in early morning.

- **Seizures**- There are many type of seizure produce in the people. Some different type of drug prevent or control them. Motor seizure, it also called as convulsions. In the sudden involuntary movement of muscles. Different type of seizure given below.
- **Myoclonic**- In the myoclonic muscles get single or multiple twitches, jerks, spasms.
- **Tonic- clonic (grand mal)** - loss the consciousness and body tone, following by

Twitching and relaxing muscles that called contraction. Loss of control of body function, such as loss of bladder control. May be short 30 second period of no breathing and persons skin may turn a shade of blue, purple, grey, white or green. After this type of seizure, a person may be sleepy and experience headaches, confusion, weakness, numbness and sore muscles.

- **Sensory**-The changes in sensation, vision, smell and or hearing without losing conscious.
- **Complex partial-** It is cause loss of awareness or partial or total loss of consciousness. It is associated with repetitive, unintentional movement such as twitching.
- Nausea,

- Vomiting,
- Fatigue,
- Drowsiness,
- Sleep problem,
- Memory problems,
- Changes in ability to walk or perform daily activities.

Symptoms that may be specific to the location of tumour include:

- Pressure or headache near tumour.
- Loss of balance and difficulty with fine motor skills is linked with tumour in cerebellum.

The changes in judgment. It includes loss of initiative, sluggishness, muscle weakness or paralysis in association with tumour in the frontal lobe of cerebrum. Loss of vision is partial or complete it cause tumour in frontal lobe of cerebrum.

- The change speech, hearing, moment and emotional state, such as aggressiveness and problem understanding words can develop from tumour in frontal or parietal lobe of cerebrum.
- It difficulty in look upward can cause by pineal gland tumour.
- Lactation in which the secretion of breast milk and menstrual period in women and growth in hands and feet in adult are links with pituitary gland.
- Difficulty swallowing, facial weakness or numberless or double vision can develop in brain stem. So these are all about symptoms brain tumour.[1,6,7,8]

DIAGNOSIS

MRI-In the MRI use as magnetic field. It does not use x-ray. It is produces the detail image of body. It is uses for measure size of tumours. A special dye called as contrast medium gives before scan to create medium clearer picture or image. This dye inject into patient vein to swallow. MRIs produce more detailed picture than CT scan.[8] The MRI may be of brain, spinal cord or both depending on type of tumour suspected and the likelihood that it will spread in the CNS. These are different types of MRI. The result of neuro-examination, done by internist or neurologist, helps determine which type of MRI to use.[9]

Intravenousgadolinium- enhanced MRI is used to help create picture of brain tumour. When patient first regular MRI and afterwards is given special type of contrast called gadolinium through an IV. Then, second MRI is done to get another series of picture using dye.[8]

MRI technique called diffusion weight imaging help to show the cellular structure of brain of the brain. Other technique called perfusion imaging its shows how much blood is reaching tumour. These method help to doctor predict how well treatment will work.A spinal MRI used to diagnose a tumour on near the spine.[9]

Functional MRI (**fMRI**): Primary brain tumours start in brain tissue and tend to stay there. Secondary brain tumours are more common. These cancers start somewhere else in the body and travel to the brain. Lung, breast, kidney, colon, and skin cancers are among the most common cancers that can spread to the brain.[1,8]

TREATMENT OF BRAIN TUMOUR - Brain tumours (whether primary or metastatic, benign or malignant) usually are treated with surgery, radiation, and/or chemotherapy alone or in various combinations. While it is true that radiation and chemotherapy are used more often for malignant, residual or recurrent tumours, decisions as to what treatment to use are made on a case-by-case basis and depend on a number of factors. There are risks and side effects associated with each type of therapy.[9]

(a) Surgery It is generally accepted that complete or nearly complete surgical removal of a brain tumour is beneficial for a patient. The neurosurgeon's challenge is to remove as much tumour as possible, without injuring brain tissue important to the patient's neurological function (such as the ability to speak, walk, etc).[5]

(b) Visualase Laser Thermal Ablation is a newer technique that some centers are using to treat smaller tumours particularly in areas that may be more difficult to reach using previous open surgery procedures. This involves placing a tiny catheter within the lesion, possibly completing a biopsy, then using laser to thermally ablate the lesion. This technique is only more recently used in brain tumour treatments, therefore the long term efficacy has not been established.[7]

(c) Investigational Therapies - Such therapies are given according to a protocol and include various forms of immunotherapy, therapy using targeted toxins, anti-angiogenesis therapy,

gene therapy and differentiation therapy. combinations of treatments also may be able to improve the outlook for patients, while lowering the adverse side effects.[9]

(d) Chemotherapy and radiation therapy - Radiation therapy may be recommended to destroy tumour tissue or cancer cells that cannot be surgically removed. This is done with high energy waves, such as X-ray. Sometimes chemotherapy and radiation therapy at the same time. Chemotherapy may also be done after radiation treatment.[8]

(e) Biologic drugs - Doctor may prescribe biologic drugs to boost, direct, or restore tumour. For example, the drug bevacizumab works to stop the growth of blood vessels that supply tumours.

(f) Other medications –Sometimes doctors may prescribe medications to treat symptoms and side effects caused by your brain tumour and brain cancer treatments. So these are all about treatment of brain tumour.[9,10]

IMMUNITY SYSTEM AGAINST BRAIN TUMOUR

Cytokines are major regulators of innate and adaptive immunity that enable cells of the immune system to communicate over short distances.[11] The term **cytokine** is derived from a combination of two greek words- "cyto" meaning cell and " kinos" meaning movement.[12] Cytokines are cell signalling molecules that aid cell to cell communication in immune responces an stimulate the movement of cells towards sites of inflammation, infection, andtraumma. Cytokine therapy to activate the immune system of cancer patients has been an important treatment modify.[11]

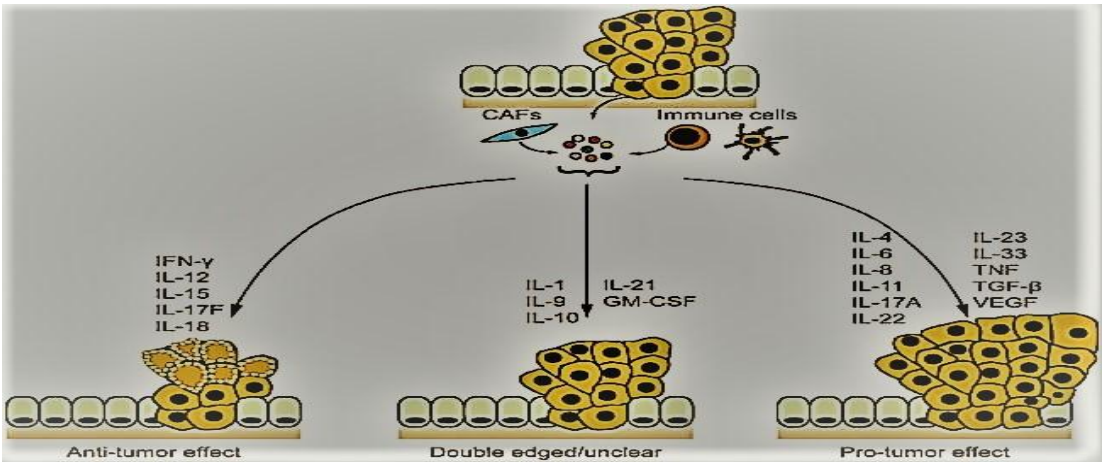
DEFINITION- Cytokines are a large group of proteins, peptides, or glycoproteins that are secreted by specific cells of immune system Cytokine are category of signalling molecules that mediate and regulate immunity, inflammation and hematoiesis. Cytokines are produced throughout the body by cells of diverse embryological origin. Cytokine is a general name; other names are defined based on their presume function, cell of secretion, or target of action. Cytokine made by lymphocytes can also be referred as lymphokines.[12]

ROLE OF CYTOKINE IN BRAIN TUMOUR

The mixture of cytokines that is produced in the cancer microenvironment has an important role in cancer pathogenesis. Cytokines that are released in responces to infection, inflammation, and immunity can function to inhibit cancer development and progression.[13]

Alternatively, cancer cells can respond to host derived cytokines that promote growth, attenuate apoptosis and facilitate invasion and metastatis. Inflammatory conditions in some tissues increases the risk of cancer,[13,14] Cytokines and chemokines are components of an intensive dialog promoting angiogenesis, metastasis, subversion of adaptive immunity and changing response to hormones and to a chemotherapeutic agent. Cytokines involved in cancer -related inflammation represents a target for innovative diagnostic and therapeutic strategies, and a future challenge for scientist and clinicians.[14]

Cytokine network in the pathogenesis of cancer.



Cytokines as a cancer therapy–(Table no 1)

Cytokines	Therapeutic action
IL-2	Enhance NK cell and CD8T cell function ; increases vascular permeability
IL-3	Enhance cancer antigen presentation
IL-4	Enhances eosinophil fiction and T-cell activation
IL-6	Enhance T-cell and B-cell function ; inhibition of IL-6 reduces lymph proliferation
IL-7	Enhance T-cell function
IL-10	Inhibits cancer antigen presentation
IL-12	Enhance Th1immunity and cytotoxicity inhibits angiogenesis
IL-13	Inhibits cytotoxicity against viral neoplasm
IL-15	Enhance cytotoxicity
IL-18	Enhance Th-1 immunity and cytotoxicity ; inhibits angiogenesis
M-CEF	Enhance Macrophage function
GM-CEF	Enhance cancer antigen presentation
IFN-a	Enhance cancer antigen presentation and cytotoxicity
IFN-y	Enhance cancer antigen presentation and cytotoxicity
TNF-a	Induce tumour cell apoptosis ; activates endothelium and granulocytes
TRAIL	Induce tumour cell apoptosis
FLT3 ligand	Stimulates dendritic-cell and NK-cell function
lymphotactin	Enhance T-cell recruitment
TGF-beta	Inhibits T-cell effector function

Cytokines and their receptor exhibit very high affinity for each other. Because of this high affinity, picomolar concentrations of cytokines can mediate a biological effect. A particular cytokine may exhibit.

Autocrine action by binding to receptor on the membrane of the same cell that secreted it.

Paracrine action binding to receptors on a target cell in close proximity to the producer cell.

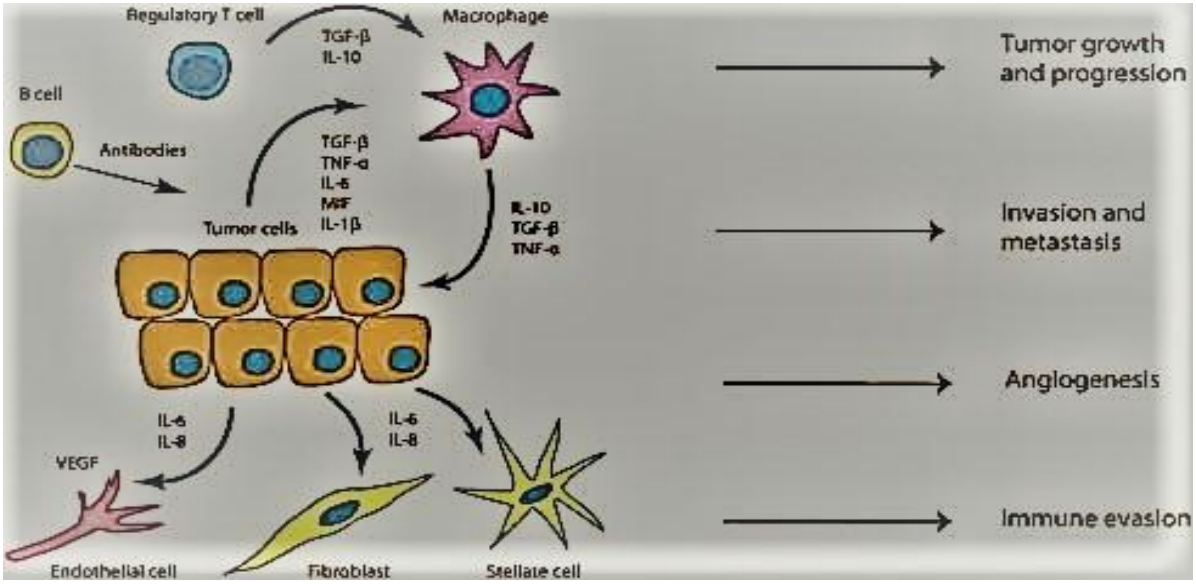
Endocrine activity by travelling through circulation and acting on target cells in distant parts of the body.[15] Cytokines are the signalling proteins which are naturally produced by white blood cells. They help mediate and fine -tune immuneresponses. Inflammation and hematopoiesis (new blood cell formation).Two types of cytokines are used to treat patients with cancer. Interferons (IFNs) and interleukins (ILs).[15,16]

General Features of Cytokines

Cytokines are secreted or membrane-bound proteins that act as mediators of intercellular signalling to regulate homeostasis of the immune system. They are produced by cells of innate and adaptive immunity in response to microbes and tumour antigens. The effects of individual cytokines on immunity depend on several factors, including the local cytokine concentration, the pattern of cytokine receptor expression and the integration of multiple signalling pathways in responding immune cells.[17] The significance of cytokines in tumour immunosurveillance has been demonstrated by the higher frequency of spontaneous cancers seen in mice genetically deficient in type I or II interferon (IFN) receptors or elements of downstream IFN receptor signal transduction.[17,18]

Cytokine signalling is characterized by a significant degree of pleiotropic, in which one cytokine has the ability to act on many different cell types to mediate diverse and sometimes opposing effects (Table 1). This has proven to be one of the primary limitations to IL-2 therapy, due to the dual function of IL-2 as a potent activator of the T effector compartment as well as the T regulatory compartment. Another important property of cytokine signalling is its degree of redundancy, in which multiple cytokines have the same functional effects.(table 1) This redundancy can make the therapeutic manipulation of cytokines somewhat challenging since modification of one cytokine can be compensated by others.[18]

Mechanism of cytokine in cancer development



CYTOKINES IN CANCER DEVELOPMENT

Cytokines are released in response to diverse range of the cellular stresses including carcinogen induce injury inflection and inflammation i these setting, cytokines function to stimulate a host response that aimed to controlling the cellular stress and minimized cellular damage.[19] Whereas effective containment to the insult promotes tissue repair, the failure to the resolve the injury can lead to the persistent cytokine production to an exacerbation of tissue destruction.[19,20] As such as, host reactions to cellular stress can impact on several stages or cancer formation andprogression.

Cytokines (endogenous) in cancer pathogenesis; (Table no.2)

Cytokines	Cytokines role
IL-1	Required for tumour invasion and angiogenesis
IL-6	Required for chemically induced lymphomas
IL-12	Inhibits chemically carcinogenesis
IL-15	Promotes nature carcinogenesis
IFN-y	Inhibits chemically carcinogenesis; Inhibits lymphomas ; stat1 And rag2 inhibits carcinomas

Role of Cytokines in Immune Suppression

Cytokines are responsible for the induction of active immune responses against tumours as well as the negative regulation of immune responses in maintaining homeostasis and self-tolerance.[20] Self-tolerance is mediated by two major classes of CD4+FoxP3+ Tregs, and understanding how cytokines regulate the generation and maintenance of Tregs-and how to break this component of tolerance to achieve and maintain successful antitumour immunity—

is an important area of current investigation. An IL-10-dependent Type I T regulatory (Tr1) cell arises in the periphery upon encountering antigen in a tolerogenic environment and mediates immune suppression. In contrast, a naturally occurring CD4+FOXP3+ T cell population (nTreg) mediates immune suppression in a contact-dependent, cytokine-independent and antigen non-specific manner. Throughout the process cytokines regulate the number and functionality of these cells as well as the effector cells that fight pathogens and tumours.[20,21] It is this delicate balance between effector and regulatory T cells that is critical for influencing the rejection or progression of tumours. IL-2, transforming growth factor-β and IL-10—and probably other cytokines—have been shown to modulate the generation of Tregs and may be involved in the fine balance between effector and regulatory populations.

Another important player in the regulation of the immune system are myeloid-derived suppressor cells (MDSC), which expand during cancer, inflammation and infection.[22] This is a heterogeneous group of cells that are described to be potent suppressors of T-cell response. The activation of MDSCs has been attributed to IFN-γ, IL-4, IL-13, and TGF-beta, while expansion of MDSCs is promoted by many other factors, including GM-CSF, M-CSF, IL-6, and VEGF.[22]

CYTOKINE AND CANCER; CHEMOKINES

Chemokines have long been associated with the recruitment of leukocytes in tumours. Recent results with gene targeted mice have provided unequivocal evidence for a role of CC chemokines in carcinogenesis.[22] The contribution of chemokines to angiogenesis and tumour pro-motion has been the object of intensive investigation. A variety of chemokines, including CCL2, CXCL12, CXCL8, CXCL11, CXCL13, CCL5, CCL17, and CCL22, have been detected in neoplastic tissues as products of either tumour cell or stromal elements. CXCL11 and related molecules [CXCL2, CXCL3, or interleukin -8 (IL-8) have an important role in melanoma progression by stimulating neoplastic growth, promotinginflammation, and inducing angio-genesis. Strong evidence demonstrates that levels of CCL2 are associate with TAM accumulation and that CCL2 may play an important role in regulation of angiogenesis. Expression of chemokine receptors plays an important role in the guiding metastasis. CXCR4 is the most frequently up-regulated chemokine receptor in cancer cells and it is associated with advanced stages and metastasis.[22,23]

CYTOKINE AND CANCER

IL-6 is a key of growth -promoting and anti apoptotic inflammatory cytokine and I also one of the effectors signals of activated NF-kobo in the promotion of neoplasia. A clear pro-tumoural role for IL-6 has been demonstrated in a multiple myeloma (MM) where both an auto crime loop by bone marrow stromal cells have been reported. Human's patients with colon cancer produce high levels of IL-6. Hepatocellular carcinoma (HCC), the most common type of liver cancer, is a frequent outcome after year of chronic inflammation induced either by chronic inflection (HBV, HVC) or sustain alcohol consumption.[24]

CYTOKINE AND CANCER. IL-10,TGF-BETA,IL-23

The tumour micro environmental is generally characterized by high concentration of immunosuppressive cytokines IL-10 and TGF-beta, in advance neoplasia there is usually low level of IL-12 and defective activation of conventional Th1 immunity recent genetic evidence indicates that the IL-12 related cytokine IL-23 promotes skin carcinogenesis.IL23 promotes the differentiation of Th17 cells which orchestrates neutrophil-initiated resistance to extracellular bacteria and inflammation.[25] TGF-BETA is a tumour suppressor frequently involved in human tumours and associated with metastasis, though it can also act under certain conditions as a tumourpromoter. In a mammary carcinoma model, deficiency in the type II TGF-BETA receptor is associated with metastasis and recruitment of MDSC. The chemokines CXCL5 and CXCL12, acting on the chemokine receptor CXCR3 and CXCR4, respectively.[25,26]

CYTOKINE AND CANCER TNF AND IL-1

TNF - mediated tumour promotion can involve different pathways: a direct effect on tumour cells of low concentration of this cytokine; an interplay with the chemokine system with induction of CXCR4;stimulation of epithelial to mesenchymal transition.[26] These findings have constituted the necessary background for the development of the clinical protocols employing TNF antagonists in cancer therapy. IL-1 was shown to augment metastaasis, a finding which at the time was related to induction of adhesion molecules in target organs. In a pancreatic islet tumour model, a first wave of my-driven angiogenesis is induced by the inflammatory cyto IL-1. In an unexpected twist, IL-1 was also shown recently to play a pivotal role in the pathogenesis live cancer.[26,27]

Type I Cytokine Receptors

The Type I cytokine receptors, which include receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, share a common signalling subunit, the common γ chain (γc), that complexes with a cytokine specific moiety to initiate intracellular signals through the coordinated activity of Janus kinases (JAK) 1 and 3 and signal transducers of activated T (STAT) molecules.[27] Additional Type I cytokine receptor subgroups include the granulocyte/monocyte colony stimulating factor (GM-CSF) and IL-6 receptor families, which share a common gp130 receptor subunit that mediates complex multi-pathway signal transduction in its target cells. The gp130 signal transduction component is utilized by several receptor complexes, including IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M, cardiotrophin-1 and ciliary neurotrophic factor, that have redundant and pleiotropic effects on the immune, hematopoietic and nervous systems. Likewise, IL-3, IL-5 and GM-CSF are also recognized by receptors in a separate GM-CSF receptor subfamily which shares a common β chain that complexes with the cytokine-specific α chain.[27,28]

Type II Cytokine Receptors

The effects of IFN-α, IFN-β, IFN-γ and IL-10 are mediated by Type II cytokine receptors, which are composed of a signalling chain and a ligand binding chain. The sequences of the Type II cytokine receptors resemble tandem Ig-like domains and the intracellular segments are typically associated with a tyrosine kinase of the Janus kinase (JAK) family.[29]

Immunoglobulin Superfamily Receptors

The immunoglobulin superfamily receptors contain extracellular immunoglobulin domains and include the receptors for IL-1, IL-18, stem cell factor and monocyte colony stimulating factor. Current Cytokines in ImmunotherapyIn this section, an effort is made to include cytokines that have already advanced into clinical use or have a strong preclinical basis for demonstrating therapeutic benefit in cancer patients.[28,29]

The Interferons (IFN)

The IFNs are classified by their ability to bind to specific receptors termed Type I, Type II, and the recently-described Type III IFN receptors.[28]

Type I Interferons

Type I IFNs, which include IFN-α and IFN-β, have emerged as the most clinically useful IFNs for the treatment of cancer. They are secreted by nearly every cell in the body and are

predominantly involved in cellular immune responses against viral infections. Type I IFNs induce expression of major histocompatibility complex (MHC) class I molecules on tumour cells and mediate the maturation of a subset of dendritic cells (DC).[24-28] They can also activate cytotoxic T lymphocytes (CTLs), natural killer (NK) cells and macrophages. In addition to their immunologic effects, the Type I IFNs can exert cytostatic and possibly apoptotic effects on tumour cells as well as anti-angiogenic effects on tumourneovasculature.[26, 28] Mice with a targeted deletion of the Type I IFN receptor have a higher rate of carcinogen-induced cancer and increased tumour growth in transplantable tumour models, supporting the hypothesis that the type I IFNs are important in tumour immunosurveillance.[29]

The Type I IFNs all share the same receptor complex (INF-αR1 and INF-αR2). IFN-α and IFN-β are actually families in themselves that comprise over 20 distinct molecules classified according to their ability to activate Type I IFN receptors.[27,28] IFN-α is comprised of a group of at least twelve distinct proteins. Recombinant IFNα-2a, IFNα-2b and IFNα-2c differ by one or two amino acids and are the isoforms most commonly used in the clinic.[28] Since IFN-α and IFN-β signal through the same receptor, they would be expected to have similar biologic effects and have overlapping indications. This prediction has not, however, been confirmed clinically and the mechanism of anti-tumour activity in vivo is not completely defined for this group of IFNs.

IFNs activate the JAK-STAT signalling pathway. IFN-α and IFN-β stimulate the activity of JAK1 and TYK2 proteins, leading to STAT1 and STAT2 tyrosine phosphorylation, and ultimately induce IL-4 secretion and subsequent activation of B cells.[25, 26, 29, 30] IFN-α also causes direct apoptosis of tumour cells in a caspase-dependent manner, which may contribute to the well-known properties of type I and II IFNs to enhance tumour cell antigen expression as well as co-stimulatory and co-inhibitory receptors that are essential to the type of immune reaction resulting between tumour and effector cells.[29] At low doses, IFN-α acts as an anti-angiogenic agent.[30] While the specific mechanisms of IFN-mediated tumour rejection in animal models have not been fully elucidated, IFN-α has been the most widely investigated cytokine for human cancer treatment and may prove to be a valuable component of combinatorial strategies for immunotherapy of solid tumours.

Interleukin 7

IL-7, a member of the small four α-helix bundle family of cytokines, is one of the IL-2-related cytokines that signal through the γc receptor subunit to exert influence over T cell survival, proliferation and homeostasis. The critical role of IL-7 in T cell development is evidenced by the finding that IL-7 receptor mutations lead to an absence of T cells and the development of severe combined immunodeficiency (SCID).[27] IL-7 is a homeostatic cytokine and functions as a limiting resource that provides continuous signal to resting naïve and memory T cells.[30] During conditions of lymphopenia, IL-7 then accumulates which leads to an increase in both T cell proliferation and T cell repertoire diversity. IL-7 also plays a role in B cell development and its receptor is found on immature B cell progenitors. A potential therapeutic advantage of IL-7 over IL-2 is its selectivity for expanding CD8+ T cell populations over CD4+FOXP3+ regulatory T cells.[31] In murine models, recombinant IL-7 has been found to augment antigen-specific T cell responses after vaccination and adoptive cell therapy[29,30], and this is now being evaluated in humans through two clinical trials.[29] Another important area of investigation is the potential role of IL-7 in promoting T-cell recovery after chemotherapy or hematopoietic stem cell transplantation. Early phase clinical trials on patients with advanced malignancy have demonstrated recombinant IL-7 to be well-tolerated with limited toxicity at biologically active doses (in which the numbers of circulating CD4+ and CD8+ T cells increased by 3–4 fold), suggestive of a broad therapeutic index.

Cytokines play complex and often opposing roles in the development of the immune system, host defense, and tumour immunobiology. Thus, understanding the biological activities and mechanisms of action of these elements is central to developing cytokine-based immunotherapy in cancer treatment.

Cytokine-Antibody Fusion Molecules

A cytokine-antibody fusion molecule is a genetically engineered fusion protein consisting of an antibody with a functional cytokine and an antigen-binding site designed to deliver cytokines to the tumour microenvironment. The prototype fusion molecule has utilized various antigen-binding moieties fused to recombinant human IL-2.[30,31] The therapeutic potential of this approach has been demonstrated using a fusion construct encoding the anti-GD2 ganglioside binding site and IL-2 against a human neuroblastoma tumour in a SCID mouse model. In this system local IL-2 delivery through the fusion molecule resulted in

enhanced effector T cell responses and increased tumour cell lysis compared to systemic IL-2 delivery. The fusion molecule was also more proficient than equivalent doses of rhIL-2 in prolonging survival and, in another study, supported proliferation of lymphokine-activated killer cells. Treatment resulted in the accumulation of the fusion molecule in the tumour, which slowed tumour growth and induced a significant immune response. This effect was more pronounced when the bifunctional molecule was injected directly into the tumour, highlighting the importance of local delivery.[31] Phase I and II clinical trials of this recombinant fusion molecule in both adult melanoma and pediatric neuroblastoma patients have demonstrated its safety in patients at doses and schedules that are able to induce immune activation.[32]

PREVENTION OF BRAIN TUMOUR

We cannot prevent the brain tumour. We can reduce the risk of developing a brintumour by avoiding environment hazards such as smoking and excessive exposure to radiation So, if we are interested in preventing cancer, take comfort in the fact that simple lifestyle changes can make a difference.[33]

- Dont use tobacco -
- Eat a healthy diet -
- Maintain a healthy weight and be physically active
- Protect yourself from the sun -
- Get vaccinated -
- Avoid risky behaviors -
- Get regular medicine care -
- Avoid exposure to pesticides and insecticides -
- Avoid exposure to carcinogenic chemicals -
- Avoid smoking -
- Avoid unnecessary exposure to radiation.

So, these are prevention for brain tumour.

CONCLUSION

The generation of potent, specific, and durable anti-tumour immunity requires a variety of cytokines that regulate important functions related to the balance between tumour rejection by antigen-specific effector cells and suppressive mechanism that allow tumours to escape

immunologic detection. The cytokines are critical for tumourimmune surveillance and have demonstrated therapeutic anti-tumour activity in murine models and in the clinical treatment of several human cancers. In addition, several innovative strategies have been developed that utilize cytokines to promote effective anti-tumour immunity, including bifunctional molecules such as antibody-cytokine fusion, expression of cytokines in recombinant viral vectors, or irradiated whole tumour cells as vaccine, by PEGylation to enhance the kinetics. Cytokine have proven to be effective in the treatment of cancer and there is little doubt they will continue to play a major role in the development of cancer immunotherapy.

Conflict of interest – NO.

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