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Review Article

Biotechnology for Prospective Medical Science

Monitoring Cellular Immune Responses in Cancer Therapy

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Abstract: Cytokines are probably the most important biologically active group of molecules to be identified since the discovery of the classical endocrine hormones. Progress with the identification of new cytokine molecules is particularly fast approaching and now it is evident that cytokines are involved, at least to some extent, in most if not all physiological processes. According to the National Cancer Institute, USA, "Cancer" is a term used for sicknesses in which atypical cells divide without manage and are capable of invading different cells. Cancer is typically characterized as a heightened proliferation of cells. Cancer arises from the dysfunction of many critical cell checkpoints. By utilizing the knowledge of unique or overexpressed cell-surface antigens or receptors on tumour cells as targets, a new form of cancer therapy has evolved over the last two decades. In particular, a variety of receptors for cellular growth factors and cytokines are overexpressed on tumour cells, which may serve as targets for cancer therapy. Previous studies reported that neutralizing monoclonal antibodies either alone or attached with radionuclide or antisense oligonucleotides to some of these receptors can selectively inhibit the growth of tumour cells by evoking host immune responses. For direct tumour cell killing, antibodies or ligands have been chemically conjugated or genetically fused to plant or bacterial toxins. Current medicinal treatments for cancer, including chemotherapy consider cytokine therapy as adjuvant therapy. Being a novel therapeutic approach, cytokine therapy has proved successful in treating patients having advanced malignancies. It manipulates the immune response generating immune effector cells for eradicating solid tumours. Only after the conventional therapies like chemotherapy, surgery etc having been performed is cytokine therapy administered. Clinical trials have already been performed for the administration of TNF-α, INF-α, IL-2, IL-12. Some clinical trials have given positive results in the form of partial or complete tumour regression. This has raised hope for selecting a suitable cytokine or its combination, its dose level for treating advanced malignancies.

Keywords: Cytokines, Cancer, Immune response, Cancer therapy, Cytokine therapy.

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1. INTRODUCTION

During the past decade the study of cytokines has become central to biomedical research. Cytokines form a chemical signalling language in multicellular organisms that regulates development, tissue repair, haemopoiesis, inflammation, and immune response.[1] Cytokines are small secreted proteins which mediate and regulate immunity, infection, and haematopoiesis. They are small, structural proteins with molecular weights starting from 8-40 kDa[2]. They act *via* binding to unique membrane receptors, which then signal the intracellular machinery *via* secondary messengers, mostly tyrosine kinases, that help regulate gene expression. Responses to cytokines include growing or reducing expression of membrane proteins (along with cytokine receptors), proliferation, and secretion of effector molecules.[3] Potent cytokine polypeptides have pleiotropic activities and functional redundancy. They act in a complex network where one cytokine can influence the production of, and response to many other cytokines. Cytokines play a critical role in tumour metastasis through interfering with tumorigenesis and progression by inhibiting tumour angiogenesis and modulation of cellular matrix[4]. Activation of T-cells *via* IL-1 ends in accelerated T-cell production of IL-2 and the associated IL-2 receptor, which in turn augments the activation of the T-cells in an autocrine loop. This effect of T-cell activation in IL-l is mimicked by TNF-alpha which is another cytokine secreted by activated macrophages[5]. The most salient and relevant residences of IL-l in infection are the initiation of cyclooxygenase 2 (COX-2), phospholipase A2 and inducible nitric oxide synthase (iNOS). Production of IL-l by using exceptional cellular sorts occurs simply in response to cellular stimulation[6]. IL-l is likewise an angiogenic factor and performs a role in tumour metastasis and blood vessel delivery. IL- 1 additionally stimulates the production of different proinflammatory cytokines like IL-6. In addition to its results on T-cells, IL-l can set off proliferation in non-lymphoid IL-2, produced and secreted through activated T-cells, is the principal interleukin responsible for clonal T-cellular proliferation[7]. IL-2, produced and secreted through activated T-cells, is the major interleukin chargeable for clonal T-cell proliferation. IL-2 also exerts effects on B-cells, macrophages, and natural killer (NK) cells. The production of IL-2 happens broadly speaking with the aid of CD4+ T-helper cells. Indeed, the IL-2 receptor is not expressed at the floor of resting T-cells and is present transiently at the floor of T-cells[8]. In contrast to T-helper cells, NK cells constitutively specific to IL-2 receptors will secrete TNF-alpha, IFN-γ and GM-CSF in reaction to IL-2, which in turn spark off macrophages. IL-2 has been used clinically in several ways. IL-6 is produced through macrophages, fibroblasts, endothelial cells and activated T-helper cells. It is a key inflammatory mediator produced with the aid of many cellular kinds. In specific, IL-6 is the primary inducer of the acute-section response in liver[9]. IL-6 additionally complements the differentiation of B-cells and their consequent production of immunoglobulin. Unlike IL-1, IL-2 and TNF-alpha, IL-6 does not now set off cytokine expression; its predominant consequences, consequently, are to augment the responses of immune cells to different cytokines[10]. In people, IL-6 is a boom aspect for myelomas, suggesting packages of IL-6 blockers.

TUMOUR NECROSIS FACTOR (TNF)

TNF-4 changed into firstly diagnosed as a cytokine liable for endotoxin prompted necrosis. Several unbiased companies suggested that treatment with recombinant TNF turned effective in opposition to several sorts of murine fashions of hepatic and pulmonary metastasis. TNF-x and TNF-D showed direct antitumor activity, killing a few tumour cells and lowering the rate of proliferation of others at the same time avoiding normal cells[11]. In the presence of TNF or TNF-B, a tumour undergoes visible haemorrhagic necrosis and tumour regression. TNF-alpha has also been shown to inhibit tumour-prompted vascularization (angiogenesis) by destroying the vascular endothelial cells within the location of a tumour, thereby reducing the glide of blood and oxygen that is essential for modern tumour boom[12]. TNF has a mighty antitumour interest against large tumour burdens in a few murine models. However, humans can most effectively tolerate 2% of the systemic TNF dose (by using weight) required in mice, because of dose restricting hypotension. High doses of TNF, administered locally through direct tumour injection can result in dramatic tumour regression in a few most cancers sufferers.

INTERFERON - (INF-Y)

Interferons are a family of proteins which can be produced with the aid of the T-cells in reaction to viral infections or stimulations with double stranded RNA, antigens, or mitogens. IFN-γ is secreted more often than not by way of CD8+ T-cells[14]. Nearly all the cells express receptors for IFN-γ and respond to IFN-γ binding by way of growing the floor expression of sophistication class I MHC proteins, thereby promoting the presentation of antigen to T-helper (CD4+) cells. Interferons have a selection of biologic residences which encompass immunomodulatory sports, antiviral activities, the ability to intervene with cell proliferation, inhibition of angiogenesis, law of differentiation, and enhancement of the expression of a diffusion of cell-surface antigens. Interferons have an antitumor hobby towards selection of tumour kinds, such as furry mobile leukaemia, chronic myelogenous leukaemia, cutaneous T-cellular lymphoma, and Kaposi's Sarcoma. Colony stimulating boom elements (CSFs) are cytokines that stimulate the proliferation of unique pluripotent stem cells of the bone marrow in adults. GM-CSF is a pleiotropic cytokine produced via some distinctive cell kinds. GM-CSF is a boom aspect for erythroid, megakaryocyte and eosinophil progenitors. IL-3 (secreted usually from T-cells) is also known as multi-CSF, because it stimulates stem cells to produce all types of hematopoietic cells. GM-CSF stimulates macrophages for antimicrobial and antitumor outcomes. GM-CSF is the pivotal mediator of the maturation and feature of dendritic cells, the maximum crucial mobile type for the induction of primary T-cellular immune responses. GM-CSF may additionally decorate Ab-dependent cellular cytotoxicity and the era and cytotoxicity of NKcells[15]. GM-CSF is a macrophage activating thing and promotes the differentiation of Langerhans cells into dendritic cells. Recombinant GM-CSF and G-CSF are an increasing number used to speed bone marrow healing after cancer chemotherapy.

NUCLEAR COMPONENT- κB (NF- κB)

Nuclear factor-κB (NF-κB) designates a collection of transcription elements defined by their potential to bind a specific DNA series first recognized in the enhancer of immunoglobulin K mild chain gene. NF-κB factors are dimensions of the Re1 circle of relatives of proteins[13]. There

are 5 individuals of the NF- κB family of transcription factors: Re1 (c-Rel), Re1 A @sixty five), Re1 B, NF-κB1 (p105lp50) and NF-κkB2 (p100lp52). Together, these proteins modify the expression of genes encoding cytokines, chemokines, adhesion molecules and antimicrobial peptides, thereby orchestrating both innate and adaptive immune responses. NF-κB/ Re1 proteins exist as homo or hetero dimers and own a conserved N-terminal Re1 homology domain (RHD) that mediates dimerization in addition to DNA binding. In most cell sorts, inactive NF-κB complexes are sequestered inside the cytoplasm through their interplay with inhibitory proteins referred to as Inhibitory kappa B (IκBs)[16]. In response to more than one stimulus, including cytokines, viral and bacterial pathogens and pressure-inducing marketers the latent cytoplasmic NF-'LBII kBa complicated is activated by means of phosphorylation on conserved series residues at the N-terminal portion of IKB; this variation happens at Ser 32 and Ser 36 in the case of I'κBa. Phosphorylation objectives IUBa for ubiquitination by using the SCF- ubiquitin ligase complex, which ends up in degradation of the inhibitory subunit with the aid of the 26s proteasome. This method activates NF-κB, which then translocate to the nucleus and binds to its cognate DNA-binding web site (five'-GGGRNNYYCC-three') in the promoter or enhancer areas of particular genes. The capacity of NF-LB to suppress apoptosis and to induce expression of proto-oncogenes along with C-myc and cyclin D1, which without delay stimulate proliferation, recommend that NF-AB may stimulate many factors of oncogenesis[17]. NF-κB also regulates the expression of diverse molecules inclusive of cell adhesion proteins, matrix metallo-proteinases, cyclooxygenase-2 (cox-2), iNos, chemokines, and inflammatory cytokines, all of which involved in tumour cellular invasion and angiogenesis. Inhibition of NF-κB abrogates tumour cellular proliferation. Although it's widely customary that inhibition of NF-AB triggers apoptosis in lots of tumour cell kinds, there are a few exceptions wherein NF-κB activation blocks malignant boom[18]. The cell cycle arrests in ordinary human epidermal cells. The cell cycle arrest by using oncogenic Ras can be bypassed by inhibition of NF-κB through the overexpression of IKB protein, which results in malignant epidermal tissues such as squamous cellular carcinoma. These findings accordingly propose that NF-κB can play a one-of-a-kind position within the law of mobile boom in tissue-context-based manner.

APOPTOSIS

Cell death is a physiological process which is required for ordinary development and life of multicellular organisms. For instance, in many cases, physiological cellular dying happens via apoptosis in preference to necrosis[19]. Abnormalities in this technique are implicated as cause or contributing thing in a variety of diseases. Inhibition of apoptosis can promote neoplastic transformation, mainly in mixture with dysregulated cellular cycle manipulation, and may have an impact on the reaction to tumour cells to anti-cancer therapy. The family of intracellular proteases, called caspases, are responsible without delay or circuitously for the morphological and biochemical modifications symbolize the phenomenon of apoptosis[20]. Diverse regulators of the caspases, inclusive of activators and inhibitors of mobile loss of life proteases are also observed. It is an important procedure in controlling tissue homeostasis in multicellular organisms. Apoptosis is occasionally called programmed cellular death (PCD) due to the fact it is a crucial part of the developmental software and is frequently the cease end result of temporal direction of cell occasions[21]. Apoptosis may be caused with the aid of a variety of stimuli together with ionizing radiations, gluco-corticoids chemotherapeutic dealers, lymphokines deprivation and diverse oxidants. Although the stimuli which set off apoptosis range markedly, the morphological functions of the manner are but conserved in special mobile sorts. It includes chromatin condensation, nuclear fragmentation, Plasma membrane blebbing, mobile shrinkage and formation of apoptotic bodies[22].

CASPASES

A family of intracellular cysteine proteases which cleave their substrates at aspanic acid residues, known as caspases. These proteases are present as inactive zymogens in basically all animal cells. In humans and mice, about 14 caspases have been recognized[23]. They can be sub grouped according to both their amino acid sequence similarities or their protease specificities. Though maximum caspases are without delay worried in cell demise, a few aren't, at least in mammals and higher eukaryotes. A subgroup of caspases, including caspase 1, 4 and 5 in humans, is involved in processing of proinflammatory cytokines including pro-interleukin- ll3 (seasoned-IL- 113), seasoned-IL- 18[24]. Many pathways for activating caspases exist, but only two were elucidated in the element. One of those centres on tumour necrosis element (TNF) circle of relative's receptors, which use caspase activation as a signalling mechanism, as a consequence connecting ligand binding at the cell floor to apoptosis induction. The difference entails the participation of mitochondria, which launch caspase activating proteins into the cytosol, thereby triggering apoptosis. The death receptor and mitochondrial pathways for caspase activation are sometimes called the extrinsic and intrinsic apoptosis pathway respectively[25]. Caspase-eight represents the apical caspase within the TNF family death receptor pathway, whereas caspase-9 serves as the apical caspase of the mitochondrial pathway. In the case of intrinsic pathway, launch of cytochrome c from mitochondria triggers caspase activation by binding to the caspase-activating protein Apaf-1. The Apaf- 1 protein usually exists as an inactive conformation within the cytosol, however on binding cytochrome c, an ATP/dATP-binding oligomerization area inside this protein mediates Apaf-l aggregation[26]. The oligomerization is complicated then binds Pro-caspase-9, and helps trans-processing of caspase-nine zymogens via the prompted proximity mechanism.

BCL-2

Apoptosis is an evolutionarily conserved cellular suicide method completed via cysteine proteases (caspases) and controlled by way of the opposing factions of the Bcl- 2 protein family[27]. They are a circle of relatives of homologous proteins, wherein a few individuals are proapoptotic and some are antiapoptotic. In human beings, 20 individuals of the Bcl- 2 family genes are actively taking part in apoptosis[28]. These genes encode the anti-apoptotic proteins, Bcl-2, Bcl-XL, Mcl- l, Bfl- l (A l), BclW and Boo (Diva) in addition to the pro-apoptotic proteins Bax, Bak, Bok (Mtd), Bad, Bid, Bim, Bik, Hrk and many others. Many Bcl-2 family proteins are constitutively localized to the membranes of mitochondria, whereas others are brought on to target those organelles in reaction to specific stimuli[29]. Caspase-8 mediated activation of Bid represents a crucial mechanism accounting for cross-

speak among the death receptor (extrinsic) and mitochondrial (intrinsic) pathway. When the Bcl-2 circle of relative proteins reach the mitochondria, they regulate the release of cytochrome c from mitochondria, with pro-apoptotic Bcl-2 family proteins inducing or making it less difficult to set off launch of this caspase activating protein and antiapoptotic participants of the own family suppressing cytochrome c release[30]. Bcl-2 family proteins have been pronounced to manipulate the discharge of other proteins from mitochondria. The proteins consist of positive caspases (caspase- 2, three and nine) which reportedly are sequestered inside mitochondria in a few kinds of cells, apoptosis inducing issue (AIF), a flavoprotein implicated in nuclear manifestations of apoptosis through caspase-unbiased mechanisms and Smac/Diablo, the inhibitor of IAP circle of relative proteins[31]. All of those proteins are encoded in the nuclear genome, transported into mitochondria, and saved in the area between the inner and outer membranes and awaiting to launch into the cytosol upon breakdown of the outer membrane.

MAP KINASE

The mitogen-activated protein kinase (MAPK) Pathway is one of the primordial signalling systems that nature has used in several variations to accomplish an amazing kind of tasks[32]. It exists in all eukaryotes, and controls such fundamental mobile techniques as proliferation, differentiation, survival and apoptosis. The simple arrangement includes a G-protein running upstream of a core module such as 3 kinases: a MAPK kinase kinase (MAPKKK) that phosphorylates and activates a MAPK[33]. Two components of this pathway, Ras and Raf, are proto-oncogenes. The most important function of this pathway pertains to growth control in all its aspects, inclusive of mobile proliferation, transformation, differentiation and apoptosis[34]. A huge type of hormones, increase elements and differentiation factors as well as tumour selling substances, hire this pathway. Most of those stimuli set off Ras proteins by inducing the change of GDP with GTP, which converts RAS into its energetic conformation. The Ras trade factor, SOS (son of sevenless), is towed to the membrane with the aid of the growth-factor-receptor-certain protein 2 adapter protein[35]. Activated Ras functions as an adapter that binds to Raf kinases with excessive affinity and causes their translocation to the cellular membrane, wherein Raf activation takes location. The Raf family of serine/threonine. Specific kinases comprise 3 contributors in higher vertebrates, A-Raf, B-Raf and C-Raf or Raf-l, which play a vital role in regulating cellular growth, differentiation and apoptosis[36]. They lie on the apex of a quite conserved protein kinase module which relays extracellular indicators to the nucleus[37]. In these modules Raf kinases phosphorylates and turns on MEK-112 which in turn phosphorylates and activates ERK-112[38]. Activated ERK-ID can then translocate to the nucleus and activate transcription elements via phosphorylation, thus changing the expression of particular genes[39]. In addition, ERK- 112 has some cytosolic substrates which have an impact on gene expression at once or not directly. Active ERK might also permit the tumour to develop its own angiogenic aid system via inducing the expression of angiogenic elements inclusive of vascular endothelial growth factor (VEGF)[40]. Activation of ERK in tumours might also permit evasion of apoptosis via inducing mobile survival. ERKs are acknowledged to play a role in mobile survival in many mobile structures[41]. In fibroblasts, ERK activation by using Raf results in a selective reduction in expression of the Bim pro-apoptotic member of the Bcl-2 circle of relatives and B-Raf over expression in fibroblasts has also been shown offer a safety towards apoptosis by using inactivating caspases after cytochrome C launch[42].

2. CONCLUSION

Cancer still remains a difficult disease to therapy and is a giant motive for morbidity and mortality. Cytotoxic capsules are very successful in killing most cancer cells; however, their performance and safety as anti-cancer therapy is confined because of the truth that these are poisonous to healthy body cells, and the mechanisms by which they inhibit is not unusual to cancer and healthy cells. Another main hassle of chemotherapy is intrinsic or acquired resistance of tumour cells against these drugs. Moreover, the use of aggregate chemotherapy is restricted as multi drug resistance may additionally get evolved. Therefore, there is a need for a therapy that can provide a higher therapeutic efficacy without causing aspect effects. Hence, efforts are being made in recent times closer to the compounds from herbal assets, to increase the effectiveness of chemotherapy and at the same time to reduce the side effects of the cytotoxic marketers.

3. AUTHOR CONTRIBUTION STATEMENT

Muktha Maganti and Manaswini Chunduru took responsibility in the conception and design of the study. Praneetha Srikonda and Khyathi Dondapati contributed substantially in compiling literature sources and drafting the manuscript. Phani Greeshma Veeramachaneni and Shaik Mohammad Anjum have provided critical revision of the article for important intellectual content. Chandrasekhar Chanda and Anupama Ammulu Manne has checked the references and given final approval of the version to be published.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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