Review Article

Cytokine Genes Polymorphism and Potential use as Bio-Markers

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ARTICLE HISTORY

ABSTRACT

Cytokines, which are recognized as signaling proteins are essential for both innate and adaptive immune response for their development and functioning, are produced by different types of cells. The expression of the cytokine gene is highly regulated and its expression and genetic polymorphisms have been applied in a variety of diseases, in treatments and in infection susceptibility. Recently it has been shown that the cytokines and their receptors are polymorphic in nature, and plays a significant role in regulating functions of normal immune system. The polymorphism that occurs in these genes are linked with a variety of immune diseases and to complications related to organ transplant. Currently the data related to disease is much contradictory and confusing, while in the analysis of cytokine the predominant form is single locus analysis. The use of polymorphic haplotype has become common as this gives the clear view about immune disfunction and the polymorphism associated the cytokine. For immune system and the traits of disease resistance, major histocompatibility complex i.e. MHC gene is considered very important. The associations of the polymorphism in autoimmune diseases, in cytokine gene, outcome of transplantation have been described. For the typing of single nucleotide polymorphism there exist several methods which could be applied for the typing of cytokine as well as variations of cytokine gene receptor. A method adopted in current study to type multiple cytokines and polymorphisms of receptor gene was SNaPshot, which is also called primer extension method. With the development we can apply this method in different laboratories in order to type cytokine SNPs in various populations and this helps in research.

INTRODUCTION

Cytokines are a family of more than hundred small proteins which functions as short range mediators, hence involved in every biological process. The cytokine field came in late 1970s when biological approaches that are molecular were introduced , which first resulted in the cloning of interferons (IFNs), initially IFNβ by Tada Taniguchi and then IFNα by David Goeddel's colleagues together with Charles Weissman's group (Feldmann, 2008).Cytokines that are secreted by cells are protein that are soluble and transmit the signals to other cells by acting as a messenger (Loo et al, 2012).There is a significant role which Cytokines plays in an immune system, and the balance between humoral Th2 and cell mediated Th1 responsiveness.Th1 cells perform its role in cellular immunity in order so they can fight against pathogens that are intracellular which includes viruses and removal of cancerous cells can occur. While in humoral immunity Th2 cells are important through the up regulation of the production of antibody, so provide protection against pathogens that are extracellular (Lan et al, 2006). Cytokines plays a significant role in the physiological processes as well as mediating the immune response. Cytokines functions by the tissue resident macrophages and also participate in organ structure maintenance and during para inflammatory state of the cells stress, restores homeostasis (Tarrant, 2010). All cells could produce and respond the cytokines except red blood cells. Today cytokines are studied in every biological discipline, hence cytokine mediated effects dominate over the different fields of immunology, inflammation, cancer and atherosclerosis (Dinarello, 2011).These regulatory cytokines could be used as biomarkers for the detection and treatment of the diseases so the more complete knowledge about the cytokines signaling is fundamental in the process of inflammation in order to find more effective clinical strategies (Van, 2009). For disease resistance traits and immune system the major histocompatibility complex, MHC gene is considered very significant. But the functions of these genes are different on traits that are economically important (Supakorn, 2009).The genes which encode MHC molecules are the most polymorphic genes that have been described in vertebrates with polymorphism that occurs at the peptide binding sites predominantly. There occurs an association between types of MHC and pathogen susceptibility (De et al, 2011). Cell surface proteins encoded by MHC genes are classified into three

categories based on molecular weight, function, and their differences in the cellular distribution (Mohammadi, 2010).Traditionally we divide the MHC genes into three classes that is the MHC class I genes, class II genes and the antigen presenting MHC molecules are encoded by them and the next is class III genes, that encodes molecules that are important in immune functions and some others that's immune function is unknown. The gene products of MHC class I and II play a significant role in immune response and in antigen presentation and in vertebrates the MHC coding genes are highly variable (Faruk et al, 2007).
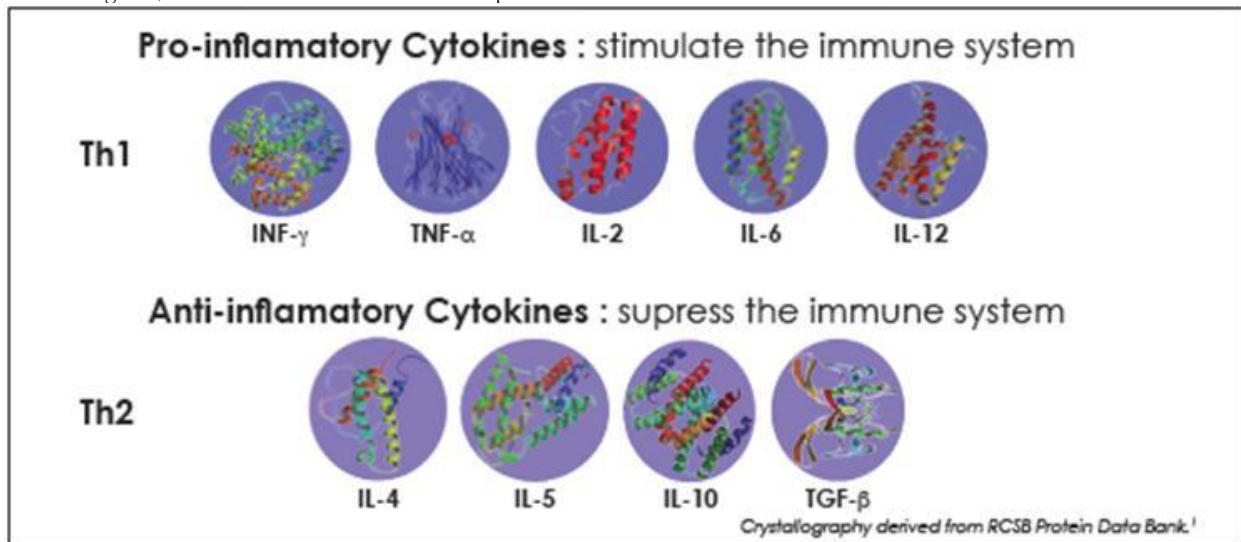
(Figure 1 : Common categories of Cytokines, www.systemicenzymesupport.org)

CHARACTERISTICS AND CLASSIFICATION OF CYTOKINES

Cytokines are involved in communication of cells, as they act as signaling proteins as well as glycoprotein. Cytokines produced by different cells are basically divided into two types i.e. Th1 and Th2. For good health there should be a balance between Th1 & Th2.Pro inflammatory response that are involved in antiviral and antibacterial responses are produced by Th1 cytokines. Uncontrolled damage of tissue could occur in case of excessive responses of Th1.In acute inflammation excess Th1 can be observed. Whereas anti inflammatory responses are produced by Th2 cytokines, as they can counteract the mediated Th1 microbicidal actions. Atopy (eczema, allergic conjunctivitis, asthma & allergic rhinitis) and allergies are associated with excessive Th2 responses. In chronic inflammation excess Th2 could be observed (www.systemicenzymesupport.org).

Cytokines consists of a large family of proteins, glycoprotein or peptides that are used in cellular communication (Olson et al, 2009). The activation, growth and differentiation of different cells are influenced by Cytokines. Cytokines exhibit less restricted tissue specificity as compared to hormones, so produced by a variety of cells types (Lumachi et al, 2010).

Cytokines have the following properties which give the shape to the nature of network (Watanabe et al, 1997)

- Pleiotropy, means single cytokine having multiple biological activities.
- Redundancy, multiple cytokines has activities of overlapping.
- Cross-talk, single cell have interactions with multiple cytokines with seems identical responses.

Other classifications are done based on structural or functional groupings. Cytokines work in a network that is highly complex and coordinated, in which they repress or induce the synthesis of their own as well as cytokine receptors and other cytokines (Bidwell et al, 1999).

CLASSIFICATION OF CYTOKINES (Ikram et al., 2004)
The growth factors include the following

- Haemopoietic growth factors
- Epidermal growth factors
- Platelet derived growth factors
- Transforming growth factor β
- Fibroblast factors
- Insulin like factors for growth
- Nerve growth factors
- Interleukins
  - IL1 to IL18
- Interferons
  - IFN- α
  - IFN- β
  - IFN- γ
- Tumour Necrosis factor(TNF) etc
- Miscellaneous

IMPORTANCE OF MHC FOR ANIMAL BREEDERS

A family of genes called Major histocompatibility complex (*MHC*) found in vertebrates mostly. MHC plays very significant role in reproductive success, immune system and in autoimmunity.

MHC encodes the protein from this gene that expressed on cell surface; these proteins display the antigen to a type of white blood cell. These white blood cells are able to coordinate in killing or kill the pathogens, malfunction or infect the cells (Supakorn , 2009). MHC is divided into the 3 main subgroups named as MHC class I genes, MHC class II genes and MHC class III genes. Heterodimeric peptide binding proteins are encoded by MHC I and MHC II , the proteins that modulate antigens loading in the lysosomal compartments are encoded by MHC class II. Other immune compartments such as heat shock proteins complement components and cytokines are encoded by MHC class III. In goat 1,077bp is the length of MHC I that encodes protein with 337 amino acids (Supakorn, 2009).

The proteins encoded by MHC-I are highly involved in presentation of peptides that are intra cellularly derived to the cytotoxic T cell. In the host control viral infection the cellular immunity is critical , an event that's highly attributable to the antigen presentation through the pathway of MHC class I, whose genes are activated transcriptionally by different cytokines or by interferons (IFN) (Jorgensen et al , 2006). Mostly the MHC genes are of particular interest for the veterinary geneticists and animal breeders because they are linked with susceptibility to a wide array of diseases and genetic resistance (Supakorn , 2009). In the genome of human the MHC, genes depends on the other genes and interacts with the other MHC as well as with non MHC genes that are located outside of the MHC region (Debnath et al, 2012).

CYTOKINES IN IMMUNITY

Cytokines are polypeptide, regulatory hormones that constitutes the signaling system of cells and are produced during the effector phases and activation of innate and specific immunity. They have many roles that are functional and serve to regulate and mediate inflammatory and immune responses (Chun, 2012). The production of the cytokines is stimulated by primary events in the response of immune system that directs the development of T helper (Th) with cytokines that are produced in discrete patterns (Garra, 1998).The expression of the Cytokine gene is highly aberrant and regulated from genetic and environmental polymorphism has been applied in susceptibility to infections, in a variety of diseases and response to the treatment (Smith et al, 2009). In malfunctioning or infecting cell or in the killing of pathogens the MHC gene is thought to be very significant gene for system of immune. By analyzing the polymorphisms of the fragments that are regulatory fragments will gave us a significant data related to gene expression and regulation. The variation of quantitative traits that controlled genetically could affect the phenotypic performance (Supakorn, 2009).Cytokines are known as Biomarkers of immunotoxcity and they regulate the responses of immune system so pleiotropic functions are performed by them (Elsabahy and Wooley, 2013).
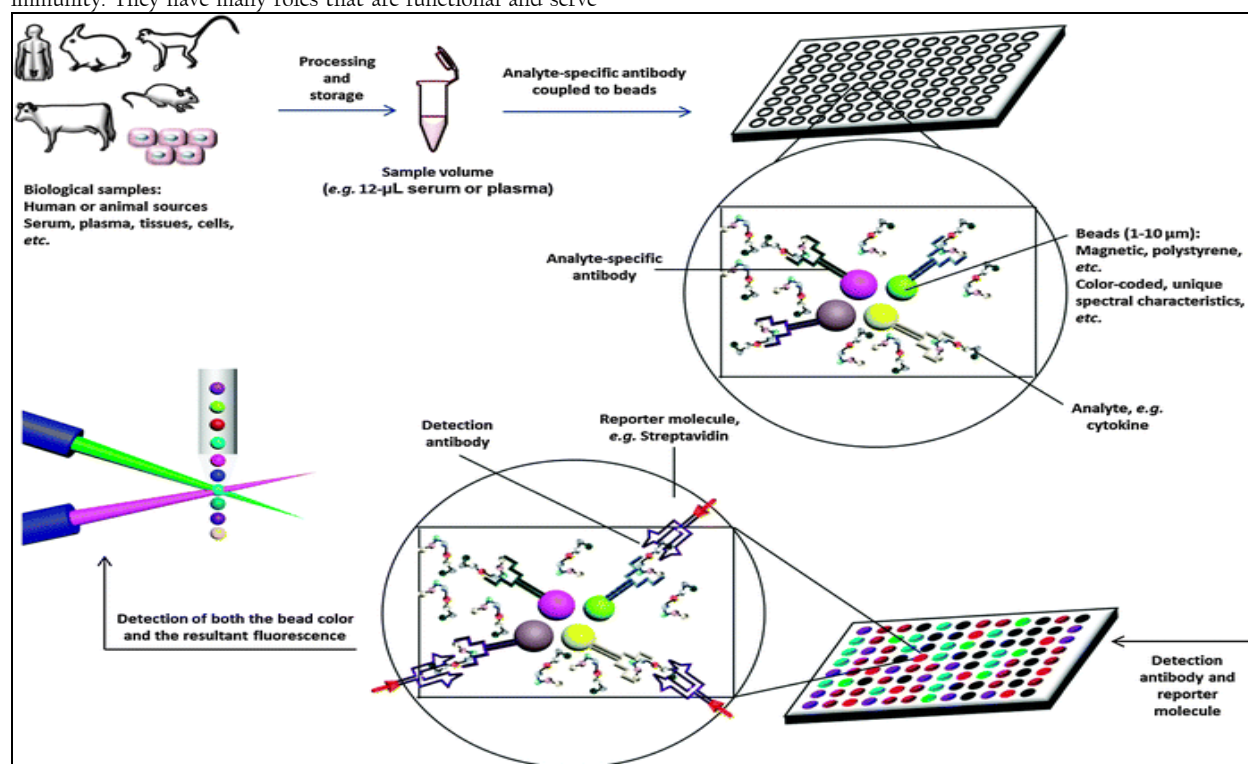
(Figure 2: Cytokines as Biomarkers of immunotoxcity, Elsabahy and Wooley, 2013).

CYTOKINE POLYMORPHISM/CYTOKINE SNP POLYMORPHISM

A series of SNPs or individual SNPs analysis in a variety of cytokine genes are involved in the disease association studies. A given cytokine is represented by single SNP through the usage of this approach. This sort of choice could be made on a number of different criteria's such as the effect on the production of cytokine, frequency in the study control population, or in other cases, the reagents availability or scientifically done prior findings. Mostly the study done of a single polymorphic locus predominates (Keen, 2002). Most of the polymorphisms that were reported within the cytokine genes occur within the regulatory or putative regions. In research, the influence of the cytokine gene polymorphisms on disease and gene expression occurs at two stages that studies using in vivo association of disease and those involving in vitro gene expression. Only very few studies have been done related to these both approaches (Lan et al, 2006). In human the SNP polymorphism results in the various levels of expression in the individuals which are healthy and has associations with autoimmunity, cardiovascular disease, susceptibility to infection and cancer. The polymorphisms related cytokine genes are not well described. We were failed to show a relationship, when we compare the polymorphisms across the regulatory regions of TNF- a gene and in vitro TNF-a release to the splenocyte in rat. Cytokine genes have various conservations across the species (Tarrant, 2010). A high rate of polymorphism as well as the associations with disease have been found using these variants in the coding region and in non coding region of cytokine gene (Smith et al, 2009).We know that Cytokines and receptors of

them are highly polymorphic. There are main three forms of poplymorphism named as microsatellites, SNPs and VNTRs. The variation occurs in polymorphism is very high. This could be easily described through the frequency by which a cytokine has been studied. The well characterize genes like IL10 and TNFa have a variety of microsatellites and single nucleotide polymorphisms (SNP), whereas the cytokines such as IL2 and IL12 previously were thought non polymorphic. Well, now in these genes polymorphism is being found (Keen, 2002).The activities of transcription are effected by Polymorphisms that are in many cytokine genes which results in the individual variations in the activity as well as the production of cytokines which ultimately affect the transplanted grafts (Brunet, 2012). Gene transcription is affected by a number of polymorphisms of the cytokine genes or gene promoters that influence the in vitro and in vivo production of cytokines (Adamopoulos et al, 2011).

This review not only describes the associations of diseases but also related to cytokine functions and to the receptors of cytokine gene polymorphism. Functional SNPs that affect gene expression, mRNA stability or structure of protein ultimately are associated with disease, and to study the controversial results related to function is also the main objective of this review (Smith et al, 2009). Polymorphisms may affect the structure of protein and if it is located in the region of regulation it may alter the protein production. In few genes small numbers of SNPs were investigated through the studies of candidate gene, previously, it is an approach that overlooks polymorphisms that are potentially important. For the typing of SNPs at large scale an approach is used that will allow the much detailed polymorphisms throughout the candidate gene and the false positive results could be found due to the increased number of SNPs typed if the data were not corrected sufficiently (Turner et al, 2002). Among individuals in pathogen resistance and in immune function, an important source of variation is represented by Cytokine polymorphism. This variation can be maintained like genotype conferred resistance to one species of pathogen and may confer the increased susceptibility to the second by exposure to a number of pathogen species. Antagonistic pleiotropy represents an example of this type of association that has been presented as a mechanism by which the genetic diversity could be found within a population (Turner et al, 2011). One host immunogenetic variation represents Cytokine gene single nucleotide polymorphisms (SNPs) and they are associated with autoimmune disorders, other diseases and response to the treatment, susceptibility to infections etc (Cano et al, 2012). The SNPs that are present in the region of regulation of the genes and code for cytokines could be modifiers of disease and also impact the expression levels. Traditionally the techniques named as PCR-RFLP were used for cytokine SNP genotyping but at large scale it is not amenable for cytokine SNP association related studies hence is a low throughput technique. Now for discrimination assay of alleles currently we use a technique called Taqman real time PCR (Johnson et al, 2004).

CYTOKINES AS DIAGNOSTIC TOOL
From inflammation to immune response, cell migration, cell growth, angiogensis, fibrosis, there is the involvement of Cytokines especially in every biological process, so we can say that in every disease there are multiple cytokines that are involved (Feldmann, 2008). There is a production of multiple cytokines in parallel or sequentially in order to coordinate evolution, initiation, and for the resolution of an immune response. Sharing bioactivities of multiple cytokines in peripheral of immune system can result in fundamental redundancy. Depending upon the presence of other cytokines,

the immunological action of a specific cytokine could be masked or enhanced. Hence, there exists such a complexity in cytokine biology that suggests that CNS action of a specific cytokine should not be considered in isolation (Quan et al, 2002). Juvenile idiopathic arthritis (JIA) is a disorder that is caused by the combination of certain genetic and environmental factors, and the all types of JIA are characterized by inflammation of the joints, hence locally the inflammation reaction is controlled by infiltration of immune cells in combination with various other cytokines. It is reported that cytokines plays significant roles in the recovery from disease (Van et al, 2009).

The rapid cellular division is very rare during adult life, and mostly it occurs as a result of an injury such as during repair of wound. The up regulation that we saw with a number of cytokines, if contrast with down regulation of cellular replication repressors like p53, occur in a wound. The cytokine expression is suppressed as the healing progresses, hence p53 is increased again. In malignant tumors there is an occurrence of rapid uncontrolled cell division (SLAVIN, 1996). During an inflammatory state the production of cytokine is mostly regulated by the activation of other cells which results in a complex cytokine cascade. The limited information is obtained by measuring single assay of cytokine, while if we want to achieve more information then there is a need to be analyzed multiple cytokines. Now with the development in technology the multiplexing of cytokines has become more fast, simple and reproducible (Vistnes et al, 2010). The abnormal productions of cytokines have been discussed in disorders of neuropsychiatric for instance Obsessive compulsive, attention deficit hyperactivity and anorexia nervosa like disorder. Cytokines play an important role in Alzheimer's disease, schizophrenia and depression and there is a common link between depression and insomnia. Cytokines are also involved in anhedonia i.e. the inability to experience pleasure and learned helplessness (Spelman et al, 2006).

CYTOKINES IN CANCER IMMUNOTHERAPY
Progress in the field of biotechnology has revealed that there are some substances which take part in immunological process between the host and the cancer, and they are monoclonal antibodies, Cytokines and the immunomodulating agents which are produced by effector cells and called as macrophages, lymphocytes and NK cells of the patients of cancer (Urushizaki 1989). The risk of cancer is enhanced by the conditions of inflammation in some tissues, and there is an involvement of cytokines in cancer related inflammation that represents a goal for therapeutic and diagnostic strategies as well as challenge for future scientists (Germano et al, 2008). The production as well as release of cytokine in cancer is affected by tumor itself or by therapeutic intervention. In fact the organ confined and systemic toxic symptoms both are mediated by the release of cytokines and there is a link between various types of cancer treatment which includes chemotherapy, radiation therapy, and hormonal therapy. So finally we conclude that cytokines play very important role in the anticancer activities. We can analyze their potential in therapeutics by this way that the direct injection of cytokines into tumors could be curative (Ronca et al, 2009). With the advancement of cytokine immunotherapy that is particularly done in combination with the chemotherapy, hence collectively called as biochemotherapy has significant improved outcome for the metastatic diseases. Now as a post surgical adjuvant Cytokines with vaccines of cancer are under trials and considered as an important part in therapy of cancer so we can achieve beneficial and long term survival rates from disease (Dezfouli et al, 2005). The advancement in molecular biology, microsequencing, and

monoclonal antibodies has made it possible to achieve the pure preparation of recombinant cytokine for the applications like therapeutics and for experimental purposes. There is a number of cytokines that perform the function of pathophysiological. The genes that are regulated by cytokines could be detected by gene chip microarray (Oppenheim, 2000).

Dendritic cells are produced from monocytes of the patients and are used in cancer vaccines. From the expression of MHC I class and MHC II class, DCs get their potential. Henc, in designing vaccines for cancer immunotherapy DCs play major role (Koido et al, 2011).
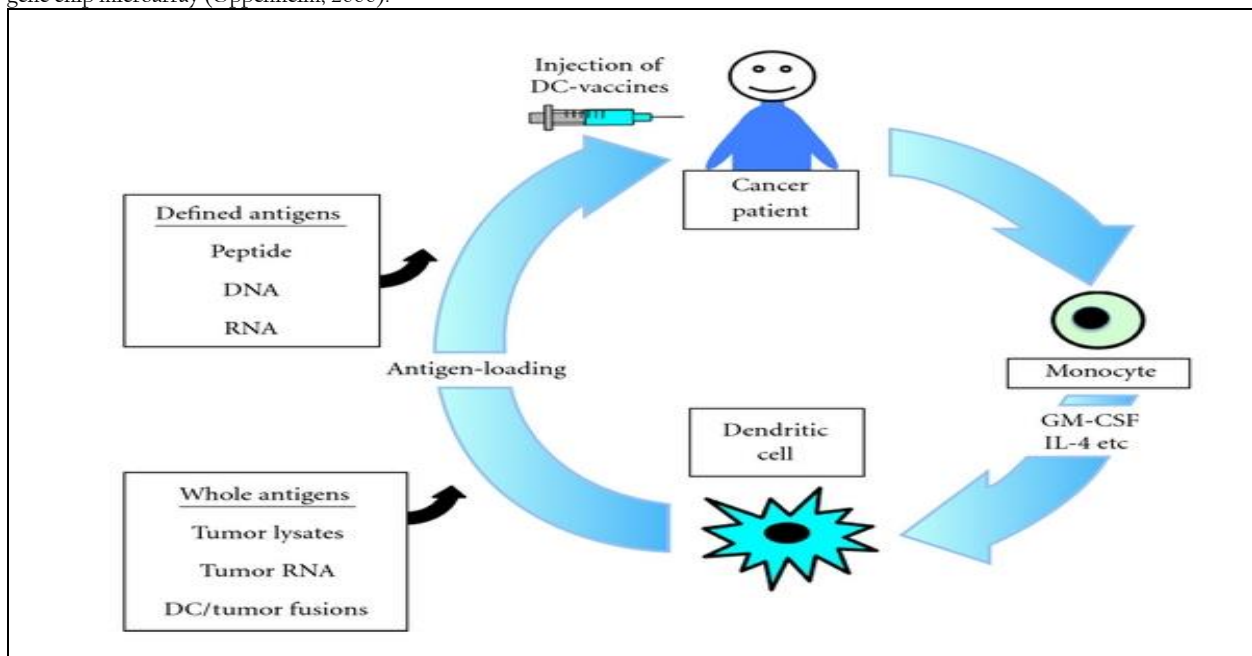

Figure 3: Role of DCs in designing vaccines for cancer immunotherapy, www.hindawi.com

CYTOKINES AS THERAPEUTIC TARGETS

The research of cytokine has introduced us with new therapies that has recognized in treating many important diseases. These therapeutic advances result in two types of strategies, the first among those embodies the administration of recombinant, purified cytokines while the second strategy is the administration of therapeutics that will inhibit dangerous affects of the up regulated and endogenous cytokines. Interferons and the Hematopoietic growth factors are the examples of successful cytokine therapeutics (Vilcek et al., 2004). Cytokines are one of the best targets for the products in biotechnology industry, they are important extracellular molecules that are rate limiting and these cytokines form very specific therapeutics; they are more specific as compared to small chemicals organic in nature due to wide surface interaction of receptors as well as antibody with the targets (Feldmann, 2008). Cytokines has potential to be used in therapeutics or immune adjuvants for certain diseases; they may be used as therapeutic targets in various diseases (Xing et al., 2000). The current review shows that the in certain pathological conditions which also includes autoimmune disease, auto-antibodies could be produced against the cytokines and that could be detected in healthy individuals. In the autoimmune diseases, these AutoAbs are prognostic markers which may be positive or negative. High levels of autoantibodies against the cytokines may cause immunodeficiency (Cappellano et al, 2012).

CYTOKINES AS BIOMARKERS

A biomarker can be defined as any measureable characteristics encompass the detection of pharmacologic, pathologic and physiologic process (Tarrant, 2010). The polymorphisms of cytokine gene could be used as markers for the clinical behavior, periodontitis susceptibility and severity. This detection offers an induction of prophylaxis and early diagnosis to other members of the family against the progression of disease (Loo et al, 2012). By studying the results of these biomarker gave us the evidence of that the change of levels of serum cytokines are linked with depression, pain, fatigue, disturbance in sleep with severity of pain and analgesic intake (Miaskowski et al, 2012). Cytokines act as very useful serum biomarkers in the patients with thyroid cancer (Lumachi et al, 2010). The chemokines, cytokines and the growth factors as biomarkers have been aided by exploratory and mechanistic studies of biomarker that insinuate repair process and inflammatory in toxicity. The cytokines are used as biomarkers because they are sensitive, specific and show temporal kinetics that permits persistence, detection, and resolution of toxicity. The use of cytokines is more useful when they derive acute toxicity named "asimmunostimulation" (Tarrant, 2010). In livestock and in human, in immune response genes the single nucleotide polymorphism (SNPs) has been recognized as markers to infectious diseases for susceptibility (Kongchum et al, 2010).

For genotyping we need a technology that should be economical and for association studies large sample size is required as well as increased number of SNP markers in cytokine genes that should be functional. For a number of significant functionally polymorphisms of cytokine in TNFa, TNFb, IL10, and IL1 genes which are associated with many inflammatory and immune diseases, Taqman real time PCR genotyping assay are validated designed (Johnson et al, 2004). For the functional analysis, the selections of SNPs were based on the proximity of a SNP to the site of transcription or association studies that were unreliable in the past. Since the studies of the functionality of SNP, the knowledge related to

gene regulatory mechanisms has been progressed and now it plays very important role. Researchers are able to case control study or re-examine the prospective for susceptibility of diseases due to the low cost platforms used for genotyping. Recently a study has been done in the patients of celiac that described a region with susceptibleness loci having both IL21 and IL 2, hence there are a number of locus for disease that are now being identified not in the genes but several hundred kilobytes away. As the technology of genotyping progresses the LD patterns will become clearer and the fine mapping of the loci will also happen. It will require new technologies and to achieve functional analysis of specific variants will take long time hence the identification of those SNPs that tag cytokine gene variant will be more easy (Smith et al, 2009). Coding sequences of MHC that are involved in immune response against the pathogens and in antigen presentation are associated with MHC marker alleles hence underlie convergent selection (Bozkaya et al, 2007).

CYTOKINES POLYMORPHISMS

With the progressively improved detection of DNA mutation, we come to know that the cytokine genes with their receptors are more polymorphic then previous studies. The analytical approaches will help to give a clear picture of polymorphisms in cytokine. These results related to association of disease and expression will be less contradicted (Keen, 2002).Cytokine and cytokine receptors are associated intrinsically to the regulation and generation of adaptive immune response and hence these are specific targets for candidate gene based genetic studies (Haralambievaa et al, 2011). There are a number of mechanisms that are for the functionality of SNP present within genes of cytokine (Smith et al, 2009). To type SNP there exist several methods and we can apply those to variation in cytokine gene and their receptors (Turner et al, 2002). In order to determine resistance or susceptibility to a myriad number of infectious diseases there is a critically involvement of MHC and MHC linked molecules. It is very interesting information that the immune molecules such as MHC and cytokine etc. acts as a key mediator of inflammation and autoimmunity are modulated by environmental factors that includes infections (Debnath et al, 2012).

CYTOKINES IN FUTURE

The expression of gene and the structure of the protein could be altered through the cytokine gene and their receptors possessing genetic variants. There exists uncertainty over the functionality of several polymorphisms and this issue could be resolved by meta-analyses or by increasing sample size. Genome wide association studies and alternative splicing on global gene expression are very helpful in order to resolve many questions related functionality of SNP, and to un reveal the SNPs promoter, allele specific chromatin immune precipitation like novel methodology will be helpful (Smith et al, 2009). An approach is required that will encompass the analysis of several polymorphisms within a single cytokine gene, due to the extent of polymorphism identified in the many cytokine genes (Keen, 2002).

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