Pathogenesis of familial mediterranean fever biology essay

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Familial Mediterranean Fever is a recessively familial systemic car inflammatory upset. The clinical symptoms include perennial febrility and serositis, and besides cause hurting in the musculuss, venters, thorax and articulations. This monogenic upset is chiefly prevailing among the people in Eastern Mediterranean part viz. among in Jews, Armenians, Arabs and Turks. FMF is normally inherited as an autosomal recessionary property but nevertheless there are certain rare instances were the FMF is found to be dominantly inherited transmitted. High akin matrimonies and badness of certain mutants could be the molecular footing of dominant transmittal. Twin surveies in monozygotic twins have revealed that harmony rate of FMF is high as 100 % and there is less part of environmental factors in the cause of disease.

FMF is found to be caused by the mutant in the MEFV cistron (Mediterranean Fever) . MEFV cistron has 10 coding DNAs and encodes 781 amino acids with a protein merchandise pyrin. So far 152 mutants and polymorphisms have been reported in MEFV cistron and about 70 % of the FMF instances arise due to five major mutants in exon 10 viz. M694V, V726A, M680I, M694I and E148Q.

However there are certain other mutants reported in 1, 2, 3, 5 and 9 coding DNAs. Most of these mutants are found to be individual amino acerb permutation mutant and some are duplication/deletion mutants. Pyrin is a multi sphere protein and is expressed in monocytes, dendritic cells, synovial fibroblasts and granulocytes. Pyrin plays an of import function in ordinance of assorted procedures such as programmed cell death, redness, and besides in ordinance of cytokines. In polymorphonuclear cells, pyrin maps as a down regulator of redness.

Surveies on pyrin construction and map have given elucidation and penetrations about the pathogenesis of FMF. The N-terminal pyrin sphere is found in many proteins and besides the amino acid sequences are about similar in these proteins, these proteins undergo protein-protein interactions and originate the programmed cell death and inflammasome. The other pyrin sphere incorporating proteins which initiate inflammasome are adaptor protein and ASC.

The ASC protein which besides posses the N-terminal pyrin sphere has a of import function in Caspase-1 induction and IL-1 ? secernment. IL-1 ? secernment depends upon the N-terminal and C-terminal B30. 2 pyrin

spheres. Several surveies have found that C-terminal B30. 2 sphere is critical for FMF as many FMF mutants are found associated in this sphere. The B30.

2 sphere consist of a C-terminal SPRY sphere and N-terminal PRY Sub sphere and it binds to procaspase -1 and besides P10 and P20 catalytic fractional monetary units. It besides acts as a go-between between the pyrin and major inflammasome constituents such as NLRP1, NLRP2, NLRP3 and Caspase-5. As from earlier surveies it is known that caspase 1 plays an of import function in the proteolytic processing of inflammatory IL-1 cytokine. It was late discovered that caspase-1 besides cleaves the pyrin and activates NF-? B and a 451-residue C-terminal fragment. These consequences are consistent with the peripheral blood study from the FMF patients, were the pyrin is found to be in a cleaved signifier. Another contention about the pyrin is that whether it is a atomic factor as it is largely localized in karyon. It is besides found that there is addition there is addition in T-cell mediated unsusceptibility in patients with FMF as there is a addition in Macrophage Inflammatory protein-1? (MIP-1 ?) degrees. Therefore the MEFV cistron mutant is responsible for the clinical spectrum of FMV as it involves unconditioned immune responses by alteration of leukocyte programmed cell death, ordinance of IL-1? and activation of NF-? B.

Several research workers are now focussed on happening suited curative mark.

Section: 3

Myotonic Muscular dystrophy:

Myotonic dystrophy is the most prevailing neuro-muscular dystrophy inherited in an autosomal dominant form. The characteristic mutant in the Myotonic dystrophy involves nucleotide repetition or duplicate in the cistron, and is normally mentioned as nucleotide repetition upset.

Unlike other muscular dystrophy, Myotonic dystrophy include a muti-system upset as its clinical syndrome and it affects the skeletal musculuss, eyes, uterine smooth musculuss, bosom, gastro-intestinal smooth musculus and cardinal nervous system. Myotonic dystrophy is chiefly classified into two types with largely similar phenotypes viz. myotonic dystrophy I (Steinert ‘ s Disease) and myotonic dystrophy II (Proximal Myotonic Myopathy)

Myotonic dystrophy Type I (Steinert ‘ s Disease) :

Myotonic dystrophy I is the most common signifier of muscular dystrophy which has a prevalence of approximately 1 in 8500 people. Myotonic dystrophy I involve broad clinical characteristics and is fundamentally classified into three classs viz. mild, classical and inborn myotonic dystrophy. Myotonic dystrophy I arise due to the addition in the three repeats in the DMPK cistron. It is inherited in an autosomal dominant form and an expectancy phenomenon occurs whereby the progeny is badly affected when it has inherited the repetitions in the DMPK allelomorph from the female parent. The expectancy phenomenon occurs when the CTG repetitions in the DMPK cistron exceeds more than 35 repetitions become

unstable and is inherited more to the progeny by addition in size during miosis.

This phenomenon non merely increases the repetitions but besides enhances the disease badness and do the disease in earlier age in consecutive coevalss. Myotonic dystrophy I is caused due to the mutant in the chromosome 19 at the 3 ‘ UTR of the myotonia-dystrophica protein kinase cistron with amplified untranslated CTG repetitions and than the mutant is transcribed into RNA and is non translated into protein. The unaffected persons normally has 35 CTG repetitions while in the myotonic dystrophy patients the CTG repetitions are more than 50. Three theoretical accounts have been proposed to understand the mechanism of CTG repetitions in myotonic dystrophy viz. haploinsufi¬? ciency of DMPK, altered look of neighboring cistrons, and dominant-negative messenger RNA mutant. In the first theoretical account it ‘ s been suggested that the clinical characteristics of the disease are due to the reduced look degrees of the DMPK, although ab initio this hypothesis was consistent with the DMPK strike hard out mice surveies as they possessed cardiac abnormalcies, nevertheless DMPK reduced degree did non demo the full clinical characteristics of the myotonic dystrophy.

In the 2nd theoretical account its been proposed that the enlargement of the CTG repetitions may hold a consequence in the look degrees of DMPK and neighboring cistrons DMWD and SIX5, as the CTG enlargement is a nucleosome binding site it was suggested that it could change the chromatin construction and affect look degrees of neighboring cistrons. Several

surveies have been carried out to verify this hypothesis by mensurating the look degrees of DMPK, DMWD and SIX5 in morbid and healthy persons. Although the look degrees of DMPK were similar in the morbid and healthy persons, nevertheless the degrees of DMWD and SIX5 were non consistent in morbid and healthy persons. These consequences correlate with the hypothesis and shows engagement of other cistrons in the pathogenesis of myotonic dystrophy. In the 3rd theoretical account it was proposed that the mutant RNA transcribed from the expanded CTG repetitions is adequate to do the clinical characteristics of the disease, the back uping grounds for this hypothesis was that the DMPK and environing cistrons in decreased degrees failed to bring forth the disease clinical symptoms and besides the accretion of the CUG repetitions transcribed from CTG repetitions in the nuclei focal point. This hypothesis correlated with the surveies in the mouse theoretical account demoing the RNA addition of map has a function in pathogenesis of the myotonic dystrophy. The possible ground could be the formation of hairpin similar constructions as a consequence of CUG repetitions and the break of U-U mismatches with C-G base brace in those constructions.

Myotonic dystrophy Type II:

Myotonic dystrophy II is clinically similar and distinguishable from Myotonic dystrophy I.

It was ab initio classified into three phenotypes viz. proximal myotonic myopathy (PROMM) , myotonic dystrophy 2 (DM2) and proximal myotonic dystrophy (PDM) and posses the clinical characteristics such as myotonia, blowing, failing, cataract, intellectual, endocrinal and cardiac jobs. Myotonic

dystrophy II is besides inherited in a autosomal dominant form and besides involves the expectancy phenomena were the consecutive coevalss are badly affected and the prevalence is similar to that of DM1. Myotonic dystrophy II involves tetra-nucleotide repetition enlargement (CCTG) in the ZnF9 cistron located in the chromosome 3. Later it was found that this tetra-nucleotide repetition enlargement (CCTG) is situated in the intron1 of the ZnF9 cistron which encodes a ZnF9 protein merchandise. These CCTG repetitions varies from 75 to 11 000 CCTG repetitions with a norm of 5000 repetitions in the patients.

ZnF9 protein is a RNA-binding protein and is normally denoted as nucleic acid adhering protein. Pathogenic mechanism taking to distinct phenotypes caused by DM2 is still ill-defined and is thought to hold similar mechanism to that of DM1. It is besides suggested that like DM1, the myotonic dystrophy II besides occurs due to RNA addition map. Several surveies are still traveling on to happen the exact mechanism behind this dystrophy.

Section 2:

Type IV Hypersensitivity:

Body immune system produces an overdone immune response when it finds out a peculiar substance which can do some inauspicious consequence inside the organic structure, this type of immune responses are called as Type IV hypersensitivity.

The Type IV hypersensitivity is besides called as delayed type hypersensitivity as it takes 2-3 yearss to bring forth an immune response.

The memory T cells are responsible for production of these immune responses upon there interaction with the antigens.

Crohns disease:

Crohns disease is an inflammatory intestine upset of the gastro enteric piece of land. The clinical characteristics of the disease include abdominal hurting, diarrhea, weight loss and is normally linked with granulomas. Epidemiologic surveies show that Crohns disease is prevailing in North America and Europe with an incidence rate of 10-200 instances per 10000 people.

In Crohns disease familial factors are found to hold important function in disease pathogenesis from the twin surveies, with a incidence rate of 37. 3 in monozygotic twins and 7 % in dizygous twins. Crohns disease is a polygenic upset and is related to chromosome 5 and 10. Crohns disease is caused due to the fluctuations in ATG16L1, IRGM, NOD2 cistrons and besides due to presence of bacteriums in the gastro enteric piece of land. It was besides found that IL23R cistron signalling tracts is besides related with the immunopathogenesis of Crohns disease. The ATG16L1, IRGM, NOD2 and IL23R cistrons produces proteins which are responsible for the immune response, and fluctuation in any of the above mentioned cistrons may take to desert in the immune response, and affects the enteric cells response to the bacteriums nowadays in the bowel. As a consequence of this Crohns disease characteristic such as chronic redness and digestive jobs occurs.

Tuberculosis:

Tuberculosis is mostly caused infective disease affecting Type IV hypersensitivity. Tuberculosis affects 8-10 million people every twelvemonth.

It is caused due to the entry of Mycobacterium TB an aerophilic intracellular pathogen into the respiratory path.

Body develops cell mediated immune response when the alveolar macrophage initiates the phagocytosis of the mycobacteria. As a consequence of this Lymphocytes and activated macrophages triggers a granulomas formation. In some instances the organic structure ‘ s immune response destroys the bacteriums inside the granulomas by production of cytokines by T Lymphocytes, which activates the macrophages. However in most instances bacteria corsets inside this granulomas and subsequently after several old ages when the immune response in the granulomas fails its get reactivated and travel to different location through the blood watercourse. Due to this the macrophages forms epithelioid cells and multi nucleate giant cells as a consequence of the release of cytokines from the allergic T lymph cells. In this phase the cytotoxic T cells targets the macrophages which consist of the bacterial antigen. Tissue harm and other features develop upon triping of macrophages by the cytokines.

Multiple induration:

Multiple induration is an autoimmune disease that causes demyelination in the cardinal nervous system. The disease is caused due to the combination of familial and environmental factors. The prevalence of the multiple induration is about about 1. 1 and 2. 5 million instances. Multiple induration is inherited in a non-mendelian manner of heritage. The harmony rate of multiple induration in the household members were identified through twin

surveies, in monozygotic twins the prevalence rate was 25. 3 % , in dizygous twins it was 5.

4 % and in non duplicate siblings it was 2. 9 % of prevalence rate. Two campaigner parts have been associated with the patterned advance of multiple induration viz. HLA-DRB1 and IL7R (CD127) by genome broad association surveies. The chief characteristic characteristic of the disease is the development of lesions in the white affair of the nervous system. These lesions destroy the medulla sheaths which are required by the nerve cells for conveying signal urges.

An redness is besides developed in the nervous system upon entry of the T-cells through the blood-brain barrier. Normally the T-cells can non come in the blood-brain barrier unless it is been affected by some pathogens. T-cells are locked inside this barrier and T-cells wrongly mistakes medulla as foreign substance and bring forth the redness inside the cardinal nervous system.

However it is still ill-defined that whether the redness or demyelination occurs foremost in the pathogenesis of the disease.