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A REVIEW ON CURRENT TREATMENT OF FANCONI ANEMIA

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ABSTRACT

This review summarises the clinical features of Fanconi Anemia and the natural history of the disease, discusses diagnosis and management, and puts the recent molecular advances into the context of the cellular and clinical Fanconi anemia phenotype. Fanconi Anemia is a rare, genetic heterogeneous multisystem disease that is the most common congenital syndrome of marrow failure. The much increased risk of FA Patients developing leukaemia and squamous cell carcinomas makes FA an important model disease for cancer predisposition. Fanconi anemia patients are characterized by pancytopenia, congential malformations, growth delay and an increased susceptibility to the development of malignancies, particularly acute myelogenous leukemia. Fanconi anemia is caused by the genetic interruption of cellular pathway that repairs DNA interstrand crosslinks. The impaired function of this pathway, and the genetic instability that results, is considered the main pathogenic mechanism behind the disease. It is mostly autosomal (except one X-link) recessive disorder characterized by diverse congenital malformations, progressive pancytopenia and predisposition to both haematological malignancy and solid tumors. Although this highly variable phenotype makes accurate diagnosis on the basis of clinical manifestations difficult in some patients, laboratory study of chromosomal breakage induced by diepoxybutane (DEB) or other crosslinking agents provides a unique cellular marker for the diagnosis of the disorder either prenatally or postnatally. Diagnosis based on abnormal response to DNA crosslinking agents can be used to identify the pre - anemia patient as well as patients with aplastic anemia or leukemia who may or may not have the physical stigmata associated with the syndrome. This overview will present our present knowledge regarding the varied phenotypic manifestation of FA and procedures for diagnosis based upon abnormal DNA damage responses.

Chromosomal instability, especially an exposure to alkylating agents, may be shown in affected subjects and is the basis for a diagnostic test. FA can be caused by mutations is at least seven different genes.

Interaction pathways have been established, both between the FA proteins and other proteins involved in DNA damage repair, such as ATM, BRCA1 and BRCA2, thereby providing a link with other disorders in which defective DNA damage repair is a feature.

(**KEYWORD:** Chromosomal Instability, Congenital Anomalies, Hematologic Abnormalities, DNA crosslink sensitivity, Somatic mosaicism.)

INTRODUCTION

Fanconi anemia (FA) is a pathologically diverse, recessively inherited disease that typically culminates in bone marrow failure in affected individuals. Patients also display profound genome instability that correlates with cancer predisposition and may have developmental defects On a molecular level, the FA pathway represents a facet of the cellular DNA repair strategy employed to resolve DNA damage, particularly interstrand crosslinks (ICLs), which covalently link the Watson and Crick strands of the DNA. ICLs particularly affect processes that inherently require DNA unwinding and strand separation such as DNA replication and transcriptionOn a molecular level, the FA pathway represents a facet of the cellular DNA repair strategy employed to resolve DNA damage, particularly interstrand crosslinks (ICLs), which covalently link the Watson and Crick strands of the DNA. ICLs particularly affect processes that inherently require DNA unwinding and strand separation such as DNA replication and transcription The FA pathway, an essential tumor-suppressive pathway, is required for protecting the human genome from a specific type of DNA damage; namely, DNA interstrand cross-links (ICLs). In this review, we discuss the recent progress in the study of the FA pathway, such as the identification of new FANCM-binding partners and the identification of RAD51C and FAN1 (Fanconi-associated nuclease 1) as new FA pathway-related

proteins. We also focus on the role of the FA pathway as a potential regulator of DNA repair choices in response to double-strand breaks, and its novel functions during the mitotic phase of the cell cycle.Fanconi anemia (FA) is an autosomal or X-linked recessive disorder characterized by chromosomal instability, bone marrow failure, cancer susceptibility, and a profound sensitivity to agents that produce DNA interstrand cross-link (ICL). To date, 15 genes have been identified that, when mutated, result in FA or an FA-like syndrome. It is believed that cellular resistance to DNA interstrand cross-linking agents requires all 15 FA or FA-like proteins. Here, we review our current understanding of how these FA proteins participate in ICL repair and discuss the molecular mechanisms that regulate the FA pathway to maintain genome stability.

The Fanconi anemia (FA) pathway maintains genome stability through co-ordination of DNA repair of interstrand crosslinks (ICLs). Disruption of the FA pathway yields hypersensitivity to interstrand crosslinking agents, bone marrow failure and cancer predisposition. Early steps in DNA damage dependent activation of the pathway are governed by monoubiquitylation of FANCD2 and FANCI by the intrinsic FA E3 ubiquitin ligase, FANCL. Downstream FA pathway components and associated factors such as FAN1 and SLX4 exhibit ubiquitin-binding motifs that are important for their DNA repair function, underscoring the importance of ubiquitylation in FA pathway mediated repair. Importantly, ubiquitylation provides the foundations for cross-talk between repair pathways, which in concert with the FA pathway, resolve interstrand crosslink damage and maintain genomic stability.

PATHOPHYSIOLOGY OF FA

Individuals with FA exhibit numerous inherited defects, but approximately 25%–40% of FA patients are physically normal. Majority of children with FA have inherited skeletal anomalies of the thumb and forearm. The thumbs are usually smaller (hypoplastic), duplicated, or absent and the forearm radius is either reduced or absent. Several FA patients display endocrine abnormalities. More than half of FA individuals have short stature which has been associated to insufficient growth hormone production and hyperthyroidism. There are also reports of FA patients with normal stature and no obvious deficiency in growth hormone production. Abnormal glucose or insulin metabolism has also been associated with FA. While individuals with diabetes have reduced insulin levels, FA individuals generally have a higher level of serum insulin. Reports suggest that approximately 8% of individuals with FA are diabetic, while up to 72%have elevated serum insulin level. In addition, osteoporosis has also been associated with FA. Hematological abnormalities are the most predominant pathological manifestation of FA. 75%–90% of FA patients develop bone marrow failure, around the first decade of life.

In addition to bone marrow failure, most FA patients expand varying degrees of blood disease, these include aplastic anemia, myelodysplastic syndrome (MDS), or acute myeloid leukemia(AML). The risk of AML exist in FA patients is approximately 800-fold higher than that of the general population, with a median age of onset of 14 years. Recent studies have explain a common pattern of chromosomal abnormalities in FA patients with MDS or AML, implying that these abnormalities can be worthwhile predictive markers. The definite cause of these hematopoietic defects is uncertain, although increasing evidence imply an underlying hypersensitivity of FA hematopoietic cells to oxidative stress.

Although FA is especially a pediatric disease, adult FA patients who are older than 18 years, represent an increasing proportion of the entire FA patient population. This has been apply to improved management of young FA patients and a precise diagnostic testing in adults. One of the major health threats faced by adult FA patients is the risk of getting cancer. In addition to hematologic cancers, solid tumors. Mostly squamous cell cancers (SCCs) of the head and neckand cervical/gynecological cancers, occur at evidently high errates in FA patients. Approximately one-third of FA patients are noted to develop a solid tumor by their fourth decade of life. In addition to the hematological abnormalities and increased cancer predisposition, FA individuals also exhibit other clinical problems, which includes hearing loss, ear anomalies as well as reduced fertility. Lowered sperm count is reported in male FA patients, and premature menopause is reported in female patients. The rate of successful pregnancy is approximately15% among non-transplanted FA patients, although improved fertility and successful pregnancy has been reported after HSC transplantation.

EPIDEMIOLOGY

The total number of people suffering from FA has not been registered worldwide.Scientists predict that the carrier frequency (people carrying a defect in one copy of a particular FA gene, while the other copy of that same FA gene is normal) for FA in the United States of America is 1 in 181. The incidence rate, or the chance of an kid being born with FA, is about 1 in 131,000 in the U.S., with approximately 31 children born with FA each year. Fanconi anemia has been reported in all national groups. However, due to founder effects, the heterozygote frequency is greater in South African Afrikaners than in the general world population. The expected birthrates in these national groups are around 1 case per 40,000 births. The carrier frequency is about 1 case per 90 people for the Ashkenazi Jews in the United States. The male-to-female ratio is 1.2:1, though equal numbers are predicted in a disorder with over 99% autosomal recessive inheritance. Fanconi anemia has been diagnosed in patients from birth to 49 years, with a median age of 7 years. Individuals with birth defects are diagnosed at younger ages when compared to those without any birth defects.

DIAGNOSIS

A genetic test is necessary to established a diagnosis of FA. These test include:- The chromosome breakage test, which treats white blood cells of sometimes skin cells with certain chemicals to see how the chromosomes in these cells reacts mutation screening, which looks for abnormalities in specific genes that are responsible for FA . Bone marrow failure is usually apparent by the second decade of life, although it can occur later. Aplastic anemia develops with failing bone marrow. Aplastic anemia is a disease in which the bone marrow cannot produce sufficient blood cells of all types. Therefore, your doctor will want to do a complete blood count (CBS).

The CBS include measure of

-Hemoglobin, the oxygen-carrying protein in red blood cells.
-Hematocript, which is the volume of red blood cells in blood.
-Quantity (and size) of red blood cells.
-Quantity of white blood cells.
-Quantity of platelets.

Low levels of any of these blood components may signal anemia. Bone marrow aspiration (removing a small amount of the liquid portion of bone marrow through a needle) and a bone marrow biopsy (removing a small sample of bone marrow tissue through a needle) can confirm the diagnosis.

Ultra sound or magnetic resonance imaging (MRI) may be done to look at the size and location of the kidneys, to monitor for liver tumors and detect heart abnormalities.

TREATMENT

Treatment are focuses on signs, syndromes and will depends on several factors including the harshness of the disease, medical history, age and complete health. After diagnosis, the superiority of FA patients will mostly require some long term treatments.

Long term treatments includes

Stem cell transplantation (SCT)
Androgen Therapy
Gene Therapy
Synthetic Growth Factor
Surgery

Stem Cell Transplantation (SCT):- Stem Cell Transplantation results to develop completely over the last 20 years because of the weakness of the preparative regimens that reduce the dilemma of the excessive toxicities due to high sensitivity of Fanconi Anaemia patients to DNA alkylating agent and to radiation.

On the way to treat FA is to replace damage bone marrow. The healthy stem cells come from another person to replace called as “donar”. It is an Allogeneic Translation. These treatment is used to treat the blood diseases that decrease the number of healthy blood cells in the body.

In Allogeneic Translation, it will get donated stem cells in a procedure that’s like a blood transfusion. Once, the transplant is done, the new stem cells are in our body are travel to that affected bone marrow and start to making new blood cells.

Stem Cell Transplantation from an HLA-Matched sibling donar:- Transplantation from a matched sibling donar (MSD) is the best treatment option for Fanconi Anaemia patients. Actual dada reveals that 3 years Overall survival (OS) rates around 80%. The study consistently regulated on SCT in Fanconi Anaemia, including 417 patients transplanted from MSD.

STC from healthy MSD using bone marrow as the cell source, represents the first treatment choice facultative excellent OS and very good conclusion. Attention should be paid to the selection of healthy sibling Non- FA in the family. Healthy sibling carrier are mainly used as donar.

Stem Cell Transplantation from a HLA-Matched unrelated donar- In the Stem Cell Transplantation, genetic nature of this Fanconi Anaemia reduces the chances of finding a healthy MSD, and therefore transplant from a MUD is a relevant choice for FA patients. Forward to the last decade, the outcome from MUD SCT was very unsatisfactory with a reported 33% chances of survival at 3 years.

Androgen Therapy:- Since, SCT become more effective, Androgen Therapy was the ideal treatment for the patient stuffers from Fanconi Anaemia. Androgen are male hormone that can help the body to make more blood cells for long time.

Androgen, the male hormone raise the count of red blood cells and platelets count. It don’t perform as well at raising the white blood cell count. Unlike a stem cell transplantation, androgens don’t allow the bone marrow to make enough of all three types of blood cells on its own. Thus, it may need continuing treatment with androgens to control the effects of Fanconi Anaemia.

Also, androgens lose their capability to help the body to make more blood cells, which means it will need other treatments. Androgen Therapy can have serious side effects, such as liver disease. This treatment also can’t prevent the patient from developing leukemia (a type of blood cancer).

Gene Therapy:- FA is the disease which is ideal type of disease for gene therapy due to serious Hematological complications compelling SCT and the likelihood that corrected FA cells have a selective advantage over defective ones, advised by the highly recognised incidence of somatic mosaicism in FA patients. There are successful attempts accepting retroviral mediated gene

transfer in FANCC knockout mice which led to phenotype correction of MMC sensitivity. Clinical trials yet rejected in humans by using retroviral vectors, but the modern use of lentivirus vectors in knockout mice has given good results, efficient transduction could be attained using low viral dose, without cytokine prestimulation and minimal ex.

Vivo manipulation and may therefore be more successful than retroviruses in human therapy.

Synthetic Growth Factor:- Growth Factor treatment is the other way to treat FA. Growth Factor are the substances which are man made and are formed in human body. These Growth Factors helps human body to make more red blood cells and white blood cells. Growth Factor have less serious side effects than androgens.

Surgery:- FA can cause birth defects that affect the arms, thumbs, hips, legs, and other part of the body. Doctor may recommend surgery to repair some defects.

For example – A child might be born with ventricular septal defect (the defect or that hole can cause the wall seperates the lower chamber of heart. In that case, doctor suggested heart surgery to close the hole and heart can work properly.

Some children suffer from FA needs surgery of digestive system. Problems that can affect their nutrition, growth and survival.

Some people suffer from FA have the common problem which is arrived from birth, in which trachea (windpipe) which carries air to the lungs, is connected to the oesophagus, which carry food. This cause serious problems like breathing, swallowing, eating, ect. And can lead to the lungs infection. Surgery is needed to separate the two organs and allow normal eating and breathing**.**

CONCLUSION

Applicable progress in the study of genetic and pathophysiology mechanism of FA has been conclude in last few years. This progress was similar to the medical treatments. This is particularly true for the transplant setting that, admitting with some detrimental impact on the occurrence of late malignancies, definitely prolonged patients survival for the time being, these benefits could be maximized by all inclusive monitoring care plans, co-ordinated by centres with proficiency in marrow failure, that start at diagnosis and continue life- long. Future perspectives, such as small molecules, still at very preclinical stages, or gene therapy, currently at an early clinical experimental phase, are sincerely awaited for improving the quality and duration of survival of FA patients.

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