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Bloom Syndrome: an example of how genomic instability leads to cancer

Abstract

Bloom Syndrome (BS) is an autosomal recessive disorder whose phenotype consists of short height, a facial erythematous rash, UV sensitivity, microcephaly, and a narrow face. Cases have been documented all over the world but seem to be prevalent in individuals of Ashkenazic Jewish descent. The underlying cause of this condition is a mutation in the BLM gene on chromosome 15, which codes for the helicase enzyme, BLM. This protein is involved in DNA repair and acts with p53 to initiate apoptosis. Molecular analyses reveal several chromosomal breaks and sister chromatid exchanges that are around 10 times more frequent than in normal cells. These observations are thought to be a result of an alternative pathway which tries to resolve stalled replication forks during the process of DNA replication, hence sparing the cells from apoptosis. This primitive evolutionary survival mechanism allows some BS cells to survive, but at the price of an increased incidence of malignancies.

List of Abbreviations

BS	Bloom Syndrome
GH	Growth Hormone
IGF1	Insulin-like Growth Factor 1
SCE	Sister Chromatid Exchange
SDS	Standard Deviation Score
SGA	Small for Gestational Age
RTS	Rothmund-Thomson Syndrome
WS	Werner Syndrome

Introduction

Bloom syndrome (BS) is a rare autosomal recessive disorder that was first identified in 1954 by Dr David Bloom (1). One of the most notable features of BS is the short stature of affected individuals that persists throughout their lifetime. Infants are small for their gestational age (SGA) and even though the post-natal growth rate increases steadily, the overall size of the child is still significantly below that of its peers. However, other developmental milestones, including walking and talking, were recorded at similar ages to their unaffected peers. Another characteristic feature of BS is an erythematous rash along the butterfly region of the face (cheeks and nose) that is commonly seen in infancy but can appear later in life (figures 1 & 2). Individuals with BS also have an increased sensitivity to sunlight, which may turn an already present rash into a chronic lesion. Additionally, the head circumference is smaller than usual, the face is narrow, and patients have a shrill voice. Apart from their physical appearance, BS patients also have a higher predisposition to certain diseases, chiefly chronic lung disease, diabetes mellitus, thyroid imbalances and over 100 types of cancer (2–4).

The roots of this disorder can be traced to the BLM gene on chromosome 15 at the locus 15q26.1. BLM is a protein that belongs to the RecQ family of helicases. DNA helicases are enzymes that unwind DNA during the process of DNA replication.

A loss-of-function mutation in both BLM alleles renders the individual homozygous recessive for BS (Ellis et al., 1995). Defects in the RecQ helicase family can give rise to a group of autosomal recessive disorders, namely BS, Werner's Syndrome (WS), Rothmund-Thomson Syndrome (RTS). These syndromes are characterised by genetic instability and hence, the risk of developing malignancies is greatly increased (5).

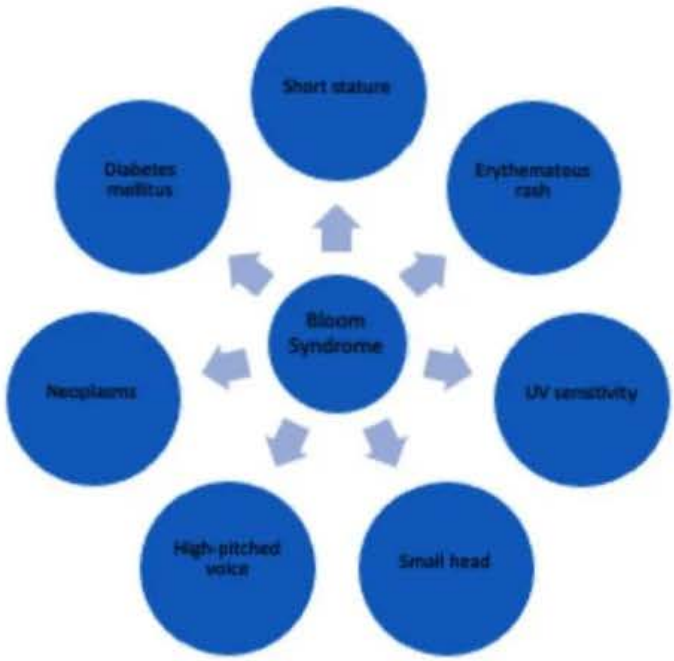

Figure 1: Common features of Bloom Syndrome

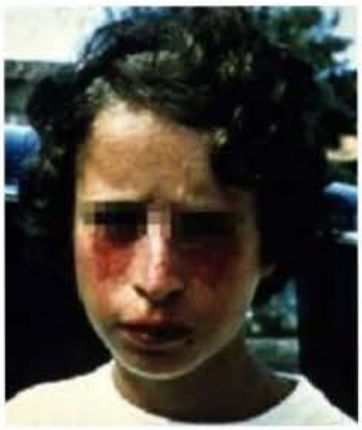

Figure 2: Child with Bloom Syndrome showing the characteristic facial erythematous rash

2. Epidemiology

Mutations in the BLM gene are prevalent in people of Ashkenazic Jewish descent (2). A genetic analysis of 1491 individuals of Ashkenazi Jewish descent with no known history of BS revealed that 1 in 107 individuals were carriers of the BLMAsh mutation. This is comparable to other conditions affecting Ashkenazic Jews such as Niemann-Pick disease (1 in 80 carrier frequency) and Fanconi Anaemia Type C (1 in 90 carrier frequency) and could lead to the inclusion of BS in screening programmes for these individuals (6). As of 2009, 26% of affected individuals known to the BS Registry are of Jewish descent, while the rest are non-Jewish (7).

3. Incidence and Types of Neoplasms in BS Patients

Individuals with BS tend to develop some form of neoplasia at an early age when compared to unaffected individuals of the same age group. In fact, it is not uncommon for children with unexplained short height and who develop rare cancers at an early age to be screened for BS. As of 1996, 100 different types of neoplasms were recorded in 71 out of 168 individuals in the Bloom Syndrome Registry. This contrasts to other syndromes that usually have a predilection for a small group of neoplasms. Interestingly, a pattern of neoplasms can be observed throughout the patients' lifetime. Leukaemias and lymphomas are the most common malignancies of childhood. Conversely, solid carcinomas are more predominant in adulthood and appear at an earlier age than in the normal population. Furthermore, patients may develop more than one primary tumour, with up to five primaries being recorded (3).

4. Molecular Basis of Disease

4.1. Chromosomal Abnormalities in BS Cells

Microscopic chromosomal analysis of BS cells reveals increased sister chromatid exchanges (SCEs) during the S-phase of the cell cycle. Sites of increased chromosomal exchange give rise to gaps and breaks in the chromosome, hence classifying BS as a chromosomal breakage syndrome.

The basis of diagnosing BS using cytogenetic analysis is a frequency of SCEs which is 10 times greater than in the normal population (8).

4.2. Proposed Roles of BML and other RecQ Helicases

The RecQ helicases unwind DNA in a 3' to 5' direction and require energy in the form of ATP. Moreover, they are the only known group of enzymes that can unwind G-quadruplex DNA. This is a highly stable structure which is formed by several planar guanine tetrads (G4) stacked on top of each other. Replication or recombination events occurring before mitosis could expose G-rich regions of DNA, thus allowing for the formation of highly stable G-tetrads instead of the usual Watson-Crick base pairs. In a normal cell, functional BLM can dissolve the tetrad, thereby allowing replication to continue. However, mutant RecQ enzymes are unable to unwind G-quadruplexes in DNA, which can halt the replication process and produce stalled recombination intermediates (9).

Additionally, BLM acts in association with human topoisomerase isozyme topo IIIα. It is thought that RecQ and topo IIIα act together during DNA recombination to stop unsuitable strands of DNA from participating in recombination events. The duo can potentially unwind the improper recombination intermediate and restore the original DNA strands (10).

4.3. BLM and Apoptosis

Several experiments done in vitro have shown that BS cells are unable to perform apoptosis properly. A study by Wang et al. found that BS fibroblasts show ineffective apoptosis mediated by p53. Interestingly, the introduction of p53 into BS fibroblasts did not improve the initiation of apoptosis. In contrast, the re-introduction of the functional BLM protein returns the sensitivity of these cells to apoptotic agents. This hints that p53 interacts with a functional BLM protein to initiate apoptosis. In fact, several DNA helicases, including BLM and WRN, were found to bind at the C-terminus of the p53 protein (11). A direct interaction between BLM and p53 may occur in nuclear bodies (NBs), as NBs are known to be involved in the regulation of apoptotic pathways. Experiments have shown that mutant BLM proteins were unable to congregate in NBs and hence disrupted p53-mediated apoptosis (11–13).

An experiment by Chester et al. demonstrated that BLM knockout mouse embryonic fibroblasts show a large burst of apoptosis early on in development, which gradually decreases with time. This could explain why individuals with BS experience a developmental delay when compared to their unaffected peers (14).

The surviving BS cells are thought to escape apoptosis by a primitive SOS-type mechanism (figure 3). In normal cells, it is common for replication forks to stall during DNA replication as they encounter a section of DNA damage. This "pause" in the replication process can be rectified with the aid of RecQ helicases, such as BLM in humans, and RecG helicase in bacteria. These proteins can recognise D-loops which form at stalled replication forks and resume the replication process by rectifying the error, without the need for chromosomal DNA breaks. If the required helicases are mutated and are unable to repair stalled replication forks, additional pathways may take over to allow the cell to escape apoptosis. This is the basis of the SOS-hypothesis and can be seen in primitive organisms like bacteria. This process involves creating chromosomal DNA breaks and the subsequent formation of D-loops. In the functional absence of certain helicases, the replication fork is restored through crossing over and genetic recombination. This mechanism explains why the BS cells that escaped apoptosis show increased chromosome breakages and hyper-recombination (15). The newly formed hyper-recombinant DNA shows a greater risk of unmasking recessive genes that can potentially cause harm, such as oncogenes. This can be achieved by either of the two mechanisms. In a heterozygous individual, a deletion of the dominant allele which is not replaced will result in hemizygosity for the recessive allele.

If the deleted dominant allele is replaced by a recessive one, the individual is rendered homozygous recessive (16).

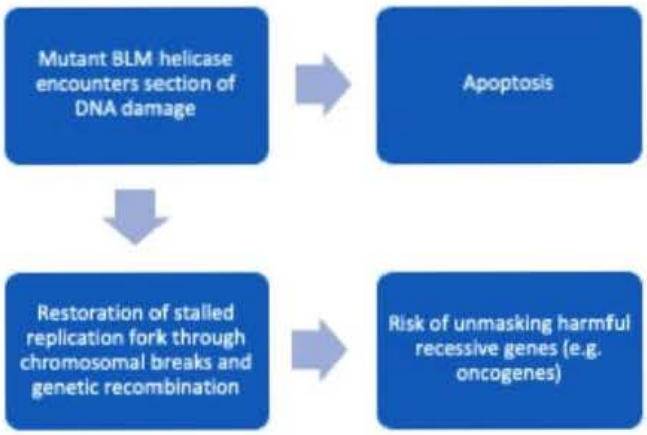

Figure 3: Flowchart showing molecular basis of BS pathogenesis

5. Other Complications

Many conditions can lead to children born SGA. While growth hormone (GH) is a popular treatment option, it is not advisable in BS and other chromosomal breakage syndromes. This is because BS patients are at an increased risk of developing neoplasms and GH treatment would encourage existing neoplasms to proliferate further. Hence, this poses a challenge for physicians treating SGA children whose disease aetiology is unknown. If an SGA child on GH treatment shows insulin-like growth factor 1 (IGF-1) levels above 2.5 Standard Deviation Score (SDS) and is showing little growth progress, one should consider checking for a mutation in the IGF1R gene.

This is because such mutations can render the individual insensitive to IGF-1. If no such mutations are present, BS and similar genetic conditions should be considered, especially if the parents of the individual are closely related (4).

As of yet, there is no cure for BS and symptomatic treatment must be tailored to the individual to avoid exacerbation of the condition. For example, chemotherapy is given at much lower doses than unaffected individuals and radiotherapy is avoided altogether. This is because BS cells lack appropriate DNA repair mechanisms, therefore DNA damage may lead to a more aggressive cancer or additional primary tumours (17).

6. Conclusion

Given these points, BS seems to be the result of evolutionary mechanisms that spare defective cells from death, resulting in various complications such as cancer, skin lesions, small size, and endocrine abnormalities (15). BS may be considered in screening programmes for populations at risk and should be considered as a potential diagnosis if SGA children not responding to GH treatment do not have an IGF1R mutation (4,6). Furthermore, a collaborative effort between medics, scientists and pharmaceutical companies is needed to raise awareness of rare diseases and to improve understanding of the underlying disease mechanisms with the hope of finding potential cures.

For this to take place, there needs to be strong patient participation, biobanking systems and curated rare disease databases (17).

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