Ageing Research Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Bloom's syndrome: Why not premature aging? A comparison of the BLM and WRN helicases

Christelle de Renty, Nathan A. Ellis*

University of Arizona Cancer Center, 1515 N. Campbell Ave., Tucson, AZ 81724, United States

ARTICLE INFO

Article history:
Received 6 April 2016
Received in revised form 17 May 2016
Accepted 19 May 2016
Available online xxx

Keywords:
Bloom's syndrome
RecQ helicases
BLM
Genomic instability
Cancer susceptibility
Aging

ABSTRACT

Genomic instability is a hallmark of cancer and aging. Premature aging (progeroid) syndromes are often caused by mutations in genes whose function is to ensure genomic integrity. The RecQ family of DNA helicases is highly conserved and plays crucial roles as genome caretakers. In humans, mutations in three RecQ genes — *BLM*, *WRN*, and *RECQL4* — give rise to Bloom's syndrome (BS), Werner syndrome (WS), and Rothmund-Thomson syndrome (RTS), respectively. WS is a prototypic premature aging disorder; however, the clinical features present in BS and RTS do not indicate accelerated aging. The BLM helicase has pivotal functions at the crossroads of DNA replication, recombination, and repair. BS cells exhibit a characteristic form of genomic instability that includes excessive homologous recombination. The excessive homologous recombination drives the development in BS of the many types of cancers that affect persons in the normal population. Replication delay and slower cell turnover rates have been proposed to explain many features of BS, such as short stature. More recently, aberrant transcriptional regulation of growth and survival genes has been proposed as a hypothesis to explain features of BS.

Contents

* Corresponding author.
E-mail address: naellis@email.arizona.edu (N.A. Ellis).

http://dx.doi.org/10.1016/j.arr.2016.05.010
1568-1637/

1. Introduction

Genomic instability is a biological condition in which mutations accumulate in the genome at a higher rate than in normal cells. The distinction between rate and frequency is an important one, because differences in mutation frequency can be explained by differences in mutation rate or by differences in cell turnover (*i.e.*, proliferation and apoptosis rates). Genomic instability can be environmentally determined by mutagenic exposure or genetically determined by mutation of DNA damage response or DNA repair genes. It is a common feature of cancers where both mechanisms play an important role in its generation. The theoretical framework linking mutation and cancer initiation and progression is well established because somatic mutations in oncogenes and tumor suppressors are major drivers of cancer. Moreover, there are a wide variety of clinical entities associated with cancer susceptibility and caused by mutations in genes that maintain genomic integrity. There are also prominent examples of associations between genomic instability syndromes and both aging and neurological disorders. The theory linking mutation with aging or neuronal cell death dysfunction is not as well understood.

Bloom's syndrome (BS; OMIM #210900) is one of a group of rare autosomal recessive disorders characterized by chromosomal instability that includes Fanconi anemia (FA) and ataxia telangiectasia (German, 1995). As molecular analysis of mutation and gene function has advanced, clinical entities with defects in DNA damage response or DNA repair have been grouped under the rubric of genomic instability syndromes. From the clinical standpoint, the genomic instability syndromes are highly heterogeneous. The ones that are inherited as dominant traits, such as Hereditary Breast and Ovarian Cancer syndrome and Lynch syndrome, have no clinical manifestations other than cancer in the proband and in the proband's family. The genomic instability syndromes that are inherited as autosomal recessives are associated with a wide variety of clinical features of varying severity. This heterogeneity is nowhere more prominent than in the syndromes defined by mutations in the RecQ helicase family.

Genes in the RecQ helicase family are known for evolutionarily conserved regions that encode the helicase domains of the proteins. These proteins are DNA-dependent ATPases and ATP-dependent DNA unwinding enzymes. The first RecQ gene was identified in *Escherichia coli* with isolation of the *recQ1* mutant, which is resistant to thymineless death (Nakayama et al., 1984). Single RecQ genes were identified in *Saccharomyces cerevisiae* and in *Schizosaccharomyces pombe*. Isolation of the *S. cerevisiae* gene *SGS1*, for slow growth suppressor, yielded important insights because *sgs1* mutants arose as suppressors to *topoisomerase 3* (*top3*) mutations and the protein products topoisomerase III and SGS1 physically interact (Bennett et al., 2000; Gangloff et al., 1994). Besides slow growth, *top3* mutants exhibit excessive homologous recombination [HR; (Wallis et al., 1989)] as do *sgs1* mutants (Watt et al., 1996). Topoisomerase III is a type one topoisomerase that breaks and religates single-stranded DNA (ssDNA) but differs from topoisomerase I in that it acts on ssDNA more efficiently than on double-stranded DNA (dsDNA). Jim Wang postulated that *E. coli* topoisomerase III could have a function in unraveling complementary DNA strands as opposing replication forks approach each other for replication termination (Wang, 1991). This early suggestion has been supported more recently with the discovery of a role for the topoisomerase IIIα-RecQ complex in preventing ultrafine DNA bridges (UFBs; see Section 4.3) In addition to a function in replication termination, the topoisomerase IIIα-RecQ complex also possesses a unique activity that can resolve recombination intermediates without crossing-over as a decatenation enzyme (see Section 4.1). Physical or functional interactions between topoisomerase IIIs and many RecQs are evolutionarily conserved.

In humans, there are five RecQ helicase genes, presented here in the order of their discovery, namely *RECQL*, *BLM*, *WRN*, *RECQL4*, and *RECQL5*[1] (Croteau et al., 2014). During the radiation of metazoans, gene duplication produced three RecQ genes in worms and flies and five in essentially all vertebrates. Evolution has innovated distinct functions for the RecQ genes. Mutations in human *BLM* result in BS (Ellis et al., 1995). Mutations in human *WRN* and *RECQL4* are linked to Werner syndrome (WS) and Rothmund-Thomson syndrome (RTS), respectively (Kitao et al., 1999; Yu et al., 1996). Each of these syndromes features genomic instability and susceptibility to cancer, but the characteristics of the genomic instability varies and the sites and types of cancers associated with each syndrome are different. BS and RTS are early developmental disorders characterized by small size. WS is characterized by premature development of features associated with aging. While WS is classified as a segmental progeroid syndrome (Martin, 1997), the other two syndromes are not progeroid. In this review, we will present BS and its clinical features, review BLM functions in various aspects of DNA metabolism, and we will conclude with some considerations about BS and aging.

2. Clinical features of Bloom's syndrome

The most striking clinical feature of BS is small but proportional body size (German, 1969). Birth weight for persons with BS ranges from 0.7 to 3.2 kg with mean term weights of 1.89 kg ± 0.35 kg for BS boys and 1.87 kg ± 0.35 kg for BS girls compared to 3.27 kg ± 0.44 kg and 3.23 kg ± 0.53 kg for normal boys and girls, respectively (Keller et al., 1999).[2] Mean birth lengths are similarly reduced with 43.4 cm ± 4.4 cm for BS boys and 43.8 cm ± 2.8 cm for BS girls compared to 50.5 cm ± 2.5 cm and 49.9 cm ± 2.7 cm for normal boys and girls, respectively. Means for both birth weight and birth length in BS are more than two standard deviations below normal, demonstrating that the growth retardation in BS is prenatal. With the advent of fetal ultra-sound, the small size has proven evident in early fetal development. The pathognomonic genomic instability of BS, namely elevated sister chromatid exchanges (SCEs; see Section 3.1), can be detected in fetal cells and used for prenatal diagnosis; molecular analysis of the BS gene *BLM* can also be used (Sanz and German, 2006).

Growth is retarded throughout early life and into maturity. Mean adult height is 145.5 cm ± 7.6 cm for BS males and 141.5 cm ± 6.6 cm for BS females compared to 176.8 cm ± 6.7 cm and 163.7 cm ± 6.1 cm for normal males and females, respectively (Keller et al., 1999). Current data from the Bloom's Syndrome Registry are similar, with an average adult height of 149 cm (range 128–164) for BS males and 138 cm (range 115–160) for BS females (http://weill.cornell.edu/bsr/data_from_registry/). Mean adult weights are correspondingly below normal at 41.3 kg ± 8.8 kg for BS males and 36.6 kg ± 8.6 kg for BS females compared to 68.9 kg ± 9.1 kg and 58.3 kg ± 8.1 kg for normal males and females, respectively. Body mass index at birth and during post-natal development is also well below normal but the deficit decreases into adulthood.

Although the body overall is well proportioned, the head is somewhat small and narrow relative to BS body size. The malar

[1] Due to the vagaries of human activity, there are some especially unhappy aliases in the literature for human RecQ genes. We use here the HUGO gene nomenclature committee designations.

[2] The clinical data discussed in this section originates from the Bloom's Syndrome Registry, which was established by James L. German III, M.D., in the 1960s. The Registry has served as the repository for clinical, genetic, cytogenetic, and molecular information on BS and has provided the basis for a thorough and detailed natural history of the disorder.

Please cite this article in press as: de Renty, C., Ellis, N.A., Bloom's syndrome: Why not premature aging?. A comparison of the BLM and WRN helicases. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.05.010