Published in final edited form as:

Mech Ageing Dev. 2013 ; 134(0): 159–160. doi:10.1016/j.mad.2013.04.002.

Special Issue on The Segmental Progeria Cockayne Syndrome

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In 1936, Dr. Edward Alfred Cockayne, a British pediatrician, reported on a brother and sister with a unique form of dwarfism marked by retinal atrophy and deafness (Cockayne 1936). In a follow-up evaluation of the two children ten years later, Dr. Cockayne described that the prominent features of the condition included the postnatal onset of dwarfism, cataracts, optic atrophy, mental retardation, an unusual facies and body habitus, hearing loss, and a peculiar form of fine pigmentary retinitis without the typical spicules seen in retinitis pigmentosa (Cockayne 1946). It was communicated a few years later by Drs. Neill and Dingwall that a separate patient exhibiting dwarfism, as well as microcephaly and intracranial calcification, displayed similarities with the condition progeria (Neill and Dingwell 1950). Through the efforts of many investigators since, we have come to recognize the disease that afflicted these children as Cockayne syndrome (CS), a rare, autosomal recessive, segmental premature aging disorder. Recent clinical evaluation has classified CS patients into two major categories: juvenile-onset, with varying degrees of severity (severe, moderate and mild), and adult-onset, a relatively mild form of the disease (Natale 2011). Juvenile-onset CS is characterized by photosensitivity, microcephaly, developmental delays, dwarfism, sensorineural hearing loss, contractures, skill loss (*e.g.*, in speech, walking, and eating) and gait ataxia, where the severity groups correlate with physical size, milestones met and life expectancy (*i.e.*, 5, 16 and 30 years).

Individuals suffering from CS exhibit hypersensitivity to ultraviolet (UV) sunlight, although strikingly, do not display an increased incidence of skin cancer (Nance and Berry 1992). A hallmark of the disease is that cells from CS patients perform rates of DNA repair synthesis after UV irradiation in the normal range, yet are unable to recover RNA synthesis after UV exposure in comparison to normal cells (Mayne and Lehmann 1982). This cellular characteristic is currently used as a means of diagnosing the condition, and appears to stem from a specific defect in excising DNA damage from the transcribed strand of an active gene. Indeed, it has been documented that CS fibroblasts have lost the preferential repair of active genes (so-called transcription-coupled nucleotide excision repair (TC-NER)), while the general genome repair of UV photoproducts remains intact (Venema et al. 1990). This selective defect in repair capacity has been suggested to give rise to many of the more prominent age-related pathologies, presumably by causing the induction of apoptotic cell death via transcription arrest, while preserving overall genome integrity and preventing consequent cancer development (Hoeijmakers 2009).

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Early cell fusion experiments uncovered the presence of at least two complementation groups, group A (CSA) and group B (CSB), within the classic form of the disease (Lehmann 1982). The subsequent advent of DNA repair-defective Chinese hamster ovary (CHO) cell lines permitted the cloning of the first CS gene, ERCC6 (or CSB), via a functional complementation strategy for UV resistance (Troelstra et al. 1992). The CSB protein is composed of 1493 amino acids and has sequence homology to the SWI2/SNF2 family of proteins that harbor seven helicase-like ATPase motifs. Just a few years later, ERCC8 (or CSA) was isolated using a similar complementation approach with a SV40-transformed human CS fibroblast line (Henning et al. 1995). CSA is a 396 amino acid protein that harbors five WD40 repeat motifs, which serve as a scaffold point for its various interactions. Based on the enormous efforts of many investigators over the last few decades, the predominant molecular functions of the CS proteins appear to fall into three categories: (1) to facilitate the repair of transcription blocking lesions; (2) to operate as direct regulators of gene transcription and associated stress responses; and (3) to mediate efficient global genome repair of endogenous (most likely oxidative) DNA damage. Recent studies have also revealed that the CS proteins may carry out certain aspects of these functions in both the nuclear and mitochondrial compartments (Aamann et al. 2010; Kamenisch et al. 2010).

In this Special Issue, prominent scientists who have dedicated much of their career to unraveling the molecular defect(s) that underlies CS and/or identifying effective means of diagnosing and treating the disease discuss the most current mechanistic and clinical aspects of the disorder. Dr. Vincent Laugel starts by introducing the characteristic clinical features, the various levels of severity, the diagnostic criteria, and the genetic databases of CS and related disorders. Dr. Miria Stefanini and colleagues continue the discussion of the laboratory tests used to identify CS patients, and also overview the roles of the CS proteins in TC-NER and the oxidative stress response, with a focus on the neurological abnormalities and lack of cancer predisposition. Dr. Dick Jaarsma and colleagues discuss the development and application of mouse models to characterize and understand the key pathologies associated with the loss of genes related to CS. Drs. Masafumi Saijo and Hua-Ying Fan (with Robert Lake) provide an in-depth review of the structural, biochemical, molecular and cellular features of the CSA and CSB proteins, respectively. Dr. Tinna Stevnsner and colleagues present a comprehensive picture of the protein interactome involving CSA and CSB, and what this may imply regarding their biological roles. Drs. Alan Weiner and Lucas Gray discuss the potential contribution of the evolutionarily-retained CSB-PGBD3 piggyBac fusion protein to the etiology of CS. Drs. Renier Velez-Cruz and Jean-Marc Egly present evidence supporting the notion that the most critical functions of the CS proteins are in the direct regulation of gene expression and key transcriptional networks. Drs. Bruce McKay and Miguel Cabrera overview the cellular responses to transcription-blocking lesions, highlighting the specific involvement of the CS proteins in these processes. Drs. Andriy Khobta and Bernd Epe describe the experimental data that indicate a contribution of the CS proteins to repairing a range of oxidative DNA lesions. Dr. Eugenia Dogliotti and colleagues, Drs. York Kamenisch and Mark Berneburg, and Dr. Vilhelm Bohr and colleagues review the emerging data that implicates the CS proteins, both directly and indirectly, in operating to maintain redox homeostasis and mitochondrial function. Dr. James Cleaver closes the Special Issue by touching upon each of the principle defects that

appear to underlie the disorder and addressing many key issues that still remain unsolved in the CS field, including potential therapeutic strategies.

In closing, this compendium of review articles provides investigators of all backgrounds with a broad picture of our current understanding of CS and its related disorders, namely combined xeroderma pigmentosum (XP)-CS, cerebro-oculo-facio-skeletal syndrome (COFS) and UV-sensitive syndrome (UVSS). We leave you with a few questions that we feel need to be better answered as the basic science and clinical research on CS moves forward: What are the primary molecular roles of the CS proteins, and do they contribute differentially to the different clinical pathologies? For example, are the development defects largely the result of loss of transcriptional programming, whereas the neurological abnormalities stem from impaired oxidative DNA damage processing and/or mitochondrial activity? What gives rise to the variability in disease intensity; could this stem from separation-of-function or different severity (*i.e.*, loss of function versus partial function) genetic mutations? Why in many cases do CS children appear to develop normally during the first year, but exhibit severe developmental abnormalities thereafter? Are there mildly dysfunctional CSA or CSB alleles in the general population that contribute to clinical phenotypes, such as photosensitivity, microcephaly, progressive sensorineural hearing loss, contractures, skill loss and gait ataxia? To what extent do the clinical features of CS reflect mitochondrial dysfunction, and do the functions of CSA and CSB differ between the nucleus and mitochondria? Can we strategically target the identified defects in DNA repair, transcriptional programming or mitochondrial function as strategies for treating individuals who suffer from CS?

Acknowledgments

This material was supported by the Intramural Research Program of the NIH, National Institute on Aging

References

- Aamann MD, Sorensen MM, Hvitby C, Berquist BR, Muftuoglu M, Tian J, de Souza-Pinto NC, Scheibye-Knudsen M, Wilson DM III, Stevnsner T, Bohr VA. Cockayne syndrome group B protein promotes mitochondrial DNA stability by supporting the DNA repair association with the mitochondrial membrane. *FASEB J*. 2010; 24:2334–2346. [PubMed: 20181933]
- Cockayne EA. Dwarfism with retinal atrophy and deafness. *Arch Dis Child*. 1936; 11:1–8. [PubMed: 21032019]
- Cockayne EA. Dwarfism with retinal atrophy and deafness. *Arch Dis Child*. 1946; 21:52–54.
- Henning KA, Li L, Iyer N, McDaniel LD, Reagan MS, Legerski R, Schultz RA, Stefanini M, Lehmann AR, Mayne LV, Friedberg EC. The Cockayne syndrome group A gene encodes a WD repeat protein that interacts with CSB protein and a subunit of RNA polymerase II TFIIH. *Cell*. 1995; 82:555–564. [PubMed: 7664335]
- Hoeijmakers JH. DNA damage, aging, and cancer. *N Engl J Med*. 2009; 361:1475–1485. [PubMed: 19812404]
- Kamenisch Y, Foustieri M, Knoch J, von Thaler AK, Fehrenbacher B, Kato H, Becker T, Dolle ME, Kuiper R, Majora M, Schaller M, van der Horst GT, van SH, Rocken M, Rapaport D, Krutmann J, Mullenders LH, Berneburg M. Proteins of nucleotide and base excision repair pathways interact in mitochondria to protect from loss of subcutaneous fat, a hallmark of aging. *J Exp Med*. 2010; 207:379–390. [PubMed: 20100872]
- Lehmann AR. Three complementation groups in Cockayne syndrome. *Mutat Res*. 1982; 106:347–356. [PubMed: 6185841]

- Mayne LV, Lehmann AR. Failure of RNA synthesis to recover after UV irradiation: an early defect in cells from individuals with Cockayne's syndrome and xeroderma pigmentosum. *Cancer Res.* 1982; 42:1473–1478. [PubMed: 6174225]
- Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. *Am J Med Genet.* 1992; 42:68–84. [PubMed: 1308368]
- Natale V. A comprehensive description of the severity groups in Cockayne syndrome. *Am J Med Genet A.* 2011; 155A:1081–1095. [PubMed: 21480477]
- Neill CA, Dingwall MM. A syndrome resembling progeria: A review of two cases. *Arch Dis Child.* 1950; 25:213–223. [PubMed: 14783428]
- Troelstra C, van Gool A, de Wit J, Vermeulen W, Bootsma D, Hoeijmakers JH. ERCC6, a member of a subfamily of putative helicases, is involved in Cockayne's syndrome and preferential repair of active genes. *Cell.* 1992; 71:939–953. [PubMed: 1339317]
- Venema J, Mullenders LH, Natarajan AT, van Zeeland AA, Mayne LV. The genetic defect in Cockayne syndrome is associated with a defect in repair of UV-induced DNA damage in transcriptionally active DNA. *Proc Natl Acad Sci USA.* 1990; 87:4707–4711. [PubMed: 2352945]