Retinoblastoma

A summary on RB1 gene mutations

Lewis, Steven

Biology 3451

Professor: Pamela Padilla

05/05/11

Introduction

Retinoblastoma (RB) is a potentially lethal form of cancer that develops in children. RB is caused by a mutation in the RB1 gene that is responsible for producing a protein that is used in cell cycle checkpoints. Abnormal development of the RB1 protein prevents the cell cycle checkpoint from preforming its task as a mutation regulator; in return a tumor develops in the retinal cells of the eye. Retinal cells are the cells responsible for the detection of light and color, without functional retinal cells vision can be impaired or ceased. Retinoblastoma is thought to be caused by a sporadic germinal or a non-germinal RB1 gene mutation expressed in early development. The most common recognizable symptom of Retinoblastoma is leukocoria (a white glare in the pupil), but many other symptoms can emerge. Through cooperation with ophthalmologist, pediatric oncologist, and radiation therapist, several treatment options are available depending on the stage of the cancer.

Epidemiology

Retinoblastoma typically develops in children under the age of 5 and is accountable for 4% of all cancers in children below the age of 15. Retinoblastoma affects about one in 20,000 children and is diagnosed in 250 to 350 children every year in the United States and 5000 worldwide. Developing countries in east Africa have reported survival rates as low as 30% due to the lack of treatment and overall health (Chantada). The USA reported a 90% survival rate for early detection in children due to the availability of treatment options. Retinoblastoma affects everyone equally. Retinoblastoma is not bias to gender, race, or environments. The estimated male to female ratio is 1.12 to 1. There have been very few cases of RB that have been reported over the ages of 20 and is thought to be caused by malignant transformation. Ninety percent of all children who have retinoblastoma are diagnosed with the sporadic mutation making them the first ones in their family to have the cancer. The other ten percent is caused by inheritance and usually exhibit the bilateral form of the cancer. If a parent had or has the bilateral (both eyes) form of retinoblastoma and produced offspring there is a 45% of passing it on. If a parent had or has the unilateral (one eye) form of retinoblastoma, 7% to 15% of their children could have the mutation. (Parent's Guide to Understanding Retinoblastoma)

Gene function

There are over 1000 unique mutations observed in white blood cell DNA and tumor cells of children with Retinoblastoma. Majority of the RB1 mutations are caused by premature termination (a stop codon) of the nucleotide-encoding region. This is normally caused by a single base substitution, frame-shift mutation, or splice mutations. The RB1 gene is located on chromosome 13q14.2 (refer to figure 1) and encodes for a protein (198 amino acids long) that has been found to be involved in the regulation of the G1 to S transition in the cell cycle. The RB1 gene was the first tumor suppressor gene found. The encoded protein also stabilizes chromatin to maintain the overall chromatin structure. The RB protein is phosphorylated by the cyclin-dependent kinase system before it enters into the S phase of the cell cycle. Once phosphorylated the binding activity of the protein is inhibited resulting in the loss of the protein

function to regulate the cell cycle. RB1 has been shown to play a major role in nucleotide excision repair of the cell cycle. Mutations that would normally be fixed are allowed through the checkpoints resulting in tumor formation. (Refer to figure 3)

Diagnoses and detection

There are several tests to determine Retinoblastoma in children and in embryo development. Prenatal ultrasounds can detect tumor cells developing inside the eyes or head of the embryo in the womb. There are many possible gene mutations that can occur in the unilateral non-inherited form Of RB. Only 80% of RB1 gene mutations can be detected, therefore RB1 DNA test can be very difficult and expensive to achieve correct prognosis. DNA tests can be useful and accurate for the known gene mutation associated in the inherited bilateral form or RB. If a tumor is present in a non-inherited unilateral form of RB, a sample of the tumor cell would be recommended. CT scans or MRIs can also be used to detect tumors in children that have been diagnosed with retinoblastoma.

In order for the ophthalmologist to determine the stage and progression of the cancer they use the Reese-Ellsworth classification system (refer to figure 4). The higher the group the worse the chance is of saving the eye. Children that have been detected early (before year 5) are typically diagnosed using Reese-Ellsworth groups I-III and are recommended to begin chemotherapy by the use of the two drugs, vincristine and carboplatin. Patients with more advanced forms of Retinoblastoma are typically diagnosed using Reese-Ellsworth groups IV-V and require more intensive therapies.

Symptoms

There are several symptoms of Retinoblastoma, but not all symptoms are expressed in every child with RB. Some of the more common symptoms may include: a white color of the pupil instead of the normal red color (this can be seen in flash photographs of the patient) (see Figure 5), eyes can also appear crossed or in different directions, pain or redness of the eye, enlarged or dilated pupil, blurred vision, or different colored irises. Clinical misdiagnosis occurs frequently in retinoblastoma because it has to be considered in every case of leukoria (an abnormal white reflection from the retina of the eye). Although effort has been made to accurately diagnose RB the misdiagnosis of retinoblastoma in leukoria, it is a less serious consequence than the misdiagnosis of a tumor in an eye that could be fatal.

Treatments

The most common and the most effective treatment for retinoblastoma is enucleation (surgical removal of the eye). This treatment is best utilized because retinoblastoma has been known to spread to the brain, spinal cord, and bones. This treatment option is also the cheapest to undergo and is especially used in developing countries. Enucleation is used normally used in the inherited form of retinoblastoma because of the odds of reoccurring tumors due to the mutated BR1 gene in all of the cells. The removal of the eye is the only way to be sure that it

will never spread to other parts of the body. The operation is done under general anesthesia and takes one and a half hours to complete. The entire eye is removed along with a piece of the optic nerve. Blinking and tearing are not affected by the operation. An prosthetic eye is made after the operation and is identical to the other eye. The prosthetic eye can move using the extra-ocular muscles but since the muscle is not attached directly to the prosthetic, the movement is reduced compared to the natural eye.

External beam radiation can be used to save the eyes and the vision of the patients. Although more risky, this procedure is effective at reducing the tumors. The appearance of the cancer may increase because of calcium build up at the tumor site producing a white color of the retina. The long-term effects include: cataracts, radiation retinopathy (bleeding of the retina), impaired vision, and temporal bone suppression (bones on the side of the head that grow abnormally).

Radioactive plaques can also be used to treat Retinoblastoma. These plaques are disks that are custom made to fit the patient's eyes. Radioactive isotopes of iodine-125 are added to induce the tumor with radiation. Similar to the external beam radiation treatment the long-term effects include: cataracts, radiation retinopathy, and impaired vision.

Laser therapy (photocoagulation), is a non-invasive treatment that can target the specific tumor site enabling the laser to go through the wall of the eyes instead of going through the pupil. This technique is effective at destroying small tumors, but can be combined with other treatments to effectively eliminate the larger tumors.

Gene therapy on Model organism

Gene therapy to cure Retinoblastoma is currently in development. The focus of gene therapy in RB is the use of targeted injections of the herpes simplex thyrosine kinase gene followed by administration of ganciclovir. The purpose of this process is to change the mutated DNA into normal healthy DNA by viral induction (ZHOU).

Another group of researchers out of Memphis Tennessee are studying a new novel aprouch. They are using a chemical (1-(biphenyl-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol), EDL-155 for the treatment of retinoblastoma(Nassr). In this study they use a rat as a model organism. The chemical was injected into 25 rats that had retinoblastoma. Over a 4 day period and 7 out of the twenty of the rats showed a complete depletion in there tumor tissues. EDL-155 destroys the mitochondria in the tumor cells. Leaving the non tumor cells undisturbed with no side effect found. (Nassr)

Conclusion

The effects of retinoblastoma can be devastating and costly on individuals and their family. If detected early there is a good chance of saving the child's vision. Although there is always a risk factor of inheritance from a parent with the mutation, there are many treatments to suppress

or even annihilate the cancer. By continuing to fund and support medical research a cure for retinoblastoma and other cancers is promising. For more information on symptoms and treatment options consult your physician or go to www.ncbi.nlm.nih.gov search for retinoblastoma. If you or someone you know shows any signs of retinoblastoma, don't take any risks, consult a doctor.

Works Cited

Chantada, Guillermo, Ira Dunkel, Ibrahim Qaddoumi, and Celia Antoneli. "Familial Retinoblastoma in Developing Countries." *Pediatr Blood Cancer* 52.3 (2009): n. pag. *WILEY*. Web. 5 May 2011.

GUASCONI, Valentina . "Transcription factors." *Atlas of Genetics and Cytogenetics in Oncology and Haematology*. N.p., n.d. Web. 5 May 2011. <http://atlasgeneticsoncology.org/Deep/TranscripFactorsID20043.html>.

"Medscape: Medscape Access." *Medscape: Medscape Access*. N.p., n.d. Web. 5 May 2011. <http://emedicine.medscape.com/article/1222849-overview#a0101>.

Nassr, Mohamed . "Treating Retinoblastoma in Tissue Culture and in a Rat Model with a Novel Isoquinoline Derivative." *Invest. Ophthalmol. Vis. Sci* vol. 51. 7 3813-3819 (2010): n. pag. *IOVS*. Web. 6 May 2011.

"Parent's Guide to Understanding Retinoblastoma." *Untitled Document*. N.p., n.d. Web. 5 May 2011. <http://retinoblastoma.com/retinoblastoma/frameset1.htm>.

"Retinoblastoma - Genetics Home Reference." *Genetics Home Reference - Your guide to understanding genetic conditions*. N.p., n.d. Web. 5 May 2011. <http://ghr.nlm.nih.gov/condition/retinoblastoma>.

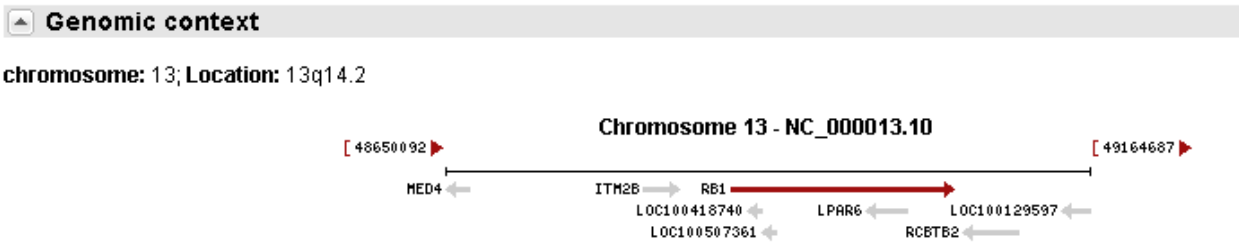
Wong, Lennie. "Cancer Incidence After Retinoblastoma Radiation Dose and Sarcoma Risk." *JAMA* 278 (1197): 1262-1267. Print.

ZHOU, YUNLI. "Further characterization of retinoblastoma gene-mediated cell growth and tumor suppression in human cancer cells." *proc. National acad. Sci. USA* 91 (1994): 4615-4619. Print.

Zhang, Mei , Graham Stevens , and Michele Madigan . "In vitro effects of radiation on human retinoblastoma cells." *International Journal of CancerVolume 96, Issue S1* Volume 96, Issue S1 (2002): n. pag. *online library*. Web. 5 May 2011.

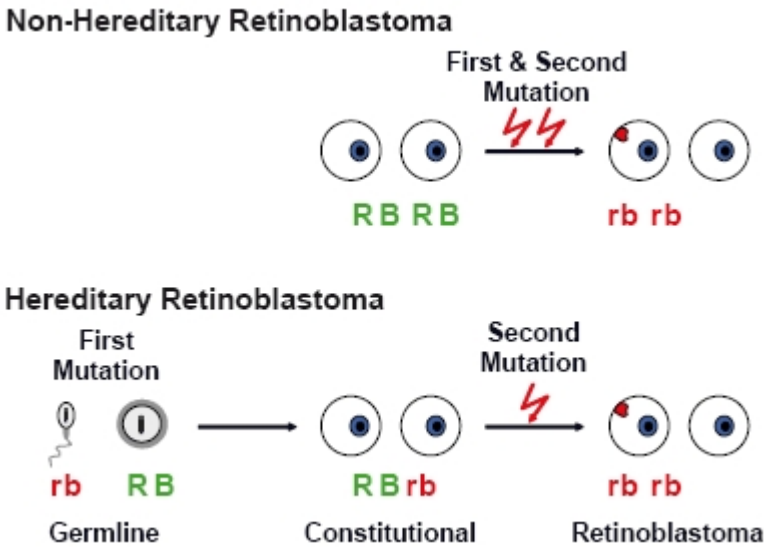
Appendix

Figure 1



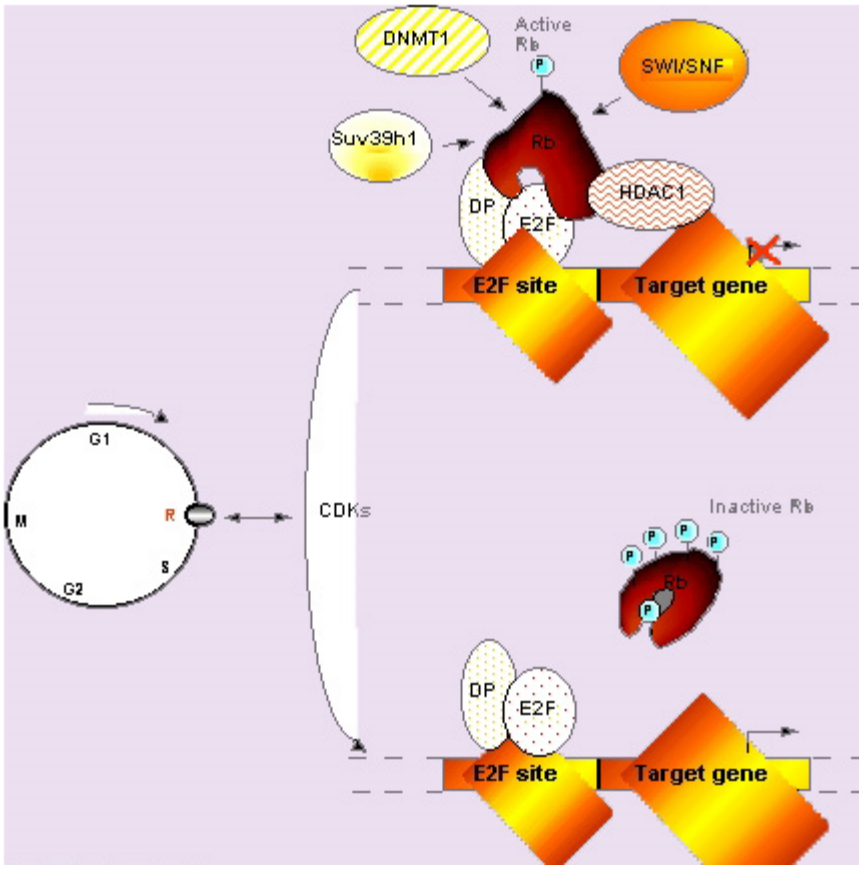
<http://www.ncbi.nlm.nih.gov/gene/5925>

Figure 2



"Retinoblastoma - Genetics Home Reference." *Genetics Home Reference - Your guide to understanding genetic conditions*. N.p., n.d. Web. 5 May 2011. <http://ghr.nlm.nih.gov/condition/retinoblastoma>.

Figure 3



<http://atlasgeneticsoncology.org/Deep/TranscripFactorsID20043.html>

Figure 4

The Reese-Ellsworth classification system

- Group I (very favorable for maintenance of sight): small solitary or multiple tumors, less than 6.4 mm in size (1 inch equals 25.4 mm), located at or below the equator of the eye.
- Group II (favorable for maintenance of sight): solitary or multiple tumors, 6.4 to 16 mm in size, located at or behind the equator of the eye.
- Group III (possible for maintenance of sight): any tumor located in front of the equator of the eye, or a solitary tumor larger than 16 mm in size and located behind the equator of the eye.
- Group IV (unfavorable for maintenance of sight): multiple tumors, some larger than 16 mm in size, or any tumor extending in front of the outer rim of the retina (ora serrata).
- Group V (very unfavorable for maintenance of sight): large tumors involving more than half of the retina, or vitreous seeding, in which small pieces of tumor are broken off and floating around the inside of the eye.

Figure 5

<http://www.stjude.org/retinoblastoma>