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Norma Andrews' Lecture Part 1:
Trypanosoma cruzi and Chagas' disease

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1. Keywords and Terms

Trypanosome, Chagas' disease, epimastigote, trypomastigote, amastigote, Southern Cone Initiative, Raduviid insects, disease vector, disease of poverty, bloodborne pathogen, protozoa

2. Lecture Notes

Trypanosoma cruzi is a protozoan parasite that causes Chagas' disease in humans. It belongs to the genus *Trypanosoma* and the family Trypanosomatidae (along with the *Leishmania* genus). *T. cruzi* is also called the American Trypanosome because it is endemic to South and Central America with 16-18 million people currently infected (April 2007). There is another species of *Trypanosoma* that is called the African Trypanosome that causes African Sleeping Sickness.

History

Carlos Chagas, while working on Malaria transmission at a rural site in Brazil, first discovered *T. cruzi*, its insect vector, animal reservoirs, and the living conditions that contribute to transmission of the disease - mud huts infested with Raduviid insects. These insects feed at night on the blood of humans and animals. Chagas dissected some of these insects and found that they carried a large protozoan that appeared in two forms – a long skinny form and a smaller form with a flagellum. He sent some of these insects to Rio de Janeiro and they infected some monkeys and found that it caused an infection and that these parasites could be found circulating in the blood. At the same time, Chagas noticed that blood taken from infected children also contained a large number of parasites.

Life Cycle

In the insect the parasite exists as the epimastigote form and lives in the digestive tract. It is shed in the feces in the trypomastigote form and can infect humans by contamination of a wound or a mucosal membrane (eye, nose, mouth, etc.). There are many cell types that can be infected in the host. When the parasite infects a cell, it transforms into the amastigote form. The epimastigote form is susceptible to complement – a part of the host immune system that functions to clear pathogens from the host – and the epimastigote is lysed by the membrane attack complex that is formed by some of the complement proteins. The trypomastigote form is resistant to complement – it isn't lysed when it enters the host.

The parasite invades a host cell via an active process, which is distinct from phagocytosis. It involves the recruitment of intracellular membranes and eventually the parasite resides inside a vacuole in the cytoplasm. Subsequently the vacuole is lysed and the parasite is released into the cytoplasm. At this point the parasite undergoes a transformation to the amastigote form and replicates via binary fission. During this time the host cell is still viable and continues to replicate – meaning that sometimes when an infected host cell divides, the daughter cell will also be infected with the parasite. The amastigote form undergoes approximately nine divisions, which takes 4-5 days, at

which point the amastigotes change back to the trypomastigote form and the cell ruptures, releasing the parasite for another round of infection.

Chagas' disease

There are two different phases of the disease that are observed. The acute phase is characterized by localized swelling at the site of entry (the eye is very common), fever, enlarged spleen, and seizures and death are possible. Death in the acute phase is usually observed in children and adults that were not exposed to the parasite as a child.

The chronic phase is characterized by immunity from re-infection but the parasite is not cleared by the immune system and symptoms don't develop until decades after the original infection. In the population that is chronically infected 40% are asymptomatic, 45% have cardiomyopathy (enlargement of the heart), and 11% have megasyndrome (enlargement of the esophagus and/or colon). The largest cause of sudden death in the chronically infected population is due to cardiomyopathy. Another very serious problem is that chronically infected people can transmit the infection through blood transfusions – especially in countries where blood is not screened.

Prevention of Human Infections

Housing improvements and insecticide spraying have proven effective in preventing human infections by controlling the vector. This has been known since the 1940s, but improvements did not occur until much later.

Even though *T. cruzi* is endemic in the southern United States and persists in a wild cycle (insects to wild animals to insects), it does not cause human infections because of superior housing. Because there are many different species of insect that are capable of transmitting the parasite and multiple vertebrate reservoirs, it is not likely that *T. cruzi* will ever be eradicated from nature. Chagas' disease is really a disease of poverty that can be effectively controlled by consistent programs of vector elimination.

The Southern Cone Initiative that was organized by the Pan-American Health Organization (PAHO) and the World Health Organization (WHO) was started in 1991 and it is focused on vector control as the means of eliminating the transmission of *T. cruzi*. So far the reduction in the incidence of Chagas' disease has been quite dramatic in some countries - in Chile, Uruguay, and Brazil a 99% reduction has been observed.

Controlling the transmission of *T. cruzi* is really a matter of political will and will be accomplished if the correct measures are taken. Even though *T. cruzi* will never be eliminated from nature, because of the large number of vertebrates that are hosts, Chagas' disease can be prevented by improved social and economical conditions. The critical issues are effective and sustained surveillance, and the development of new and less toxic drugs that can be used to treat chronically infected populations.

3. Basic Recommended Readings for the Classroom

Alberts et al. Molecular Biology of the Cell. Fifth edition. 2008. Garland Science, Taylor & Francis Group, LLC. New York. PAGES: 1508 – 1510.

Brief introduction to *T. cruzi* and Chagas' disease.

J. Wyler, editor. Modern Parasite Biology: Cellular, Immunological, and Molecular Aspects. 1990. Wilt Freeman & Company. New York. CHAPTERS: 4, 13, 17.

This is a textbook that addresses parasitic biology. Chapter 14 is on the cellular nature of *T. cruzi*. Chapter 13 is on the immunological aspects of Chagas' disease and *T. cruzi* infection. Chapter 17 is about the molecular aspects of the parasite. Even though it is dated, it is a good starting point.

Prata A. Clinical and epidemiological aspects of Chagas' disease. *Lancet Infect. Dis.* 2001. **1**(2):92-100.

This review is good and addresses many of the issues and complications of Chagas' disease. The epidemiology of the spread of disease is also addressed.

Schofield, C.J., Jannin, J., and Salvatella, R. The future of Chagas' disease control. *Trends Parasitol.* 2006. **22**(12):583-588.

This is a review that addresses the different aspects that have been taken and need to be taken in order to control Chagas' disease spread in the population. They also suggest a good way in which to approach future surveillance.

4. Review Questions

1. True/False *Leishmania* and *Trypanosoma* belong to different families.
2. Approximately how many people are infected with *T. cruzi*?
    a. 7-8 million
    b. 1-2 million
    c. 16-18 million
    d. 20-21 million
3. What is the causative agent of Chagas' disease?
    a. Leishmania amazonensis
    b. Trypanosoma cruzi
    c. Trypanosoma brucei
    d. Eschicheria coli
4. What is the vector of *T. cruzi*?
5. Circle all the different forms of *T. cruzi*.
    a. Epimastigote
    b. Deltamastigote
    c. Phylomastigote
    d. Trypomastigote
    e. Amastigote
    f. Bimastigote
6. Where does *T. cruzi* replicate in the insect?
7. Why is the epimastigote form not infectious in humans?
8. Why is the trypomastigote form infectious in humans?
9. What is the main cause of sudden death in chronically infected people with Chagas' disease?
10. What are the best ways to control the spread of *T. cruzi*?

11. True/False There are many different species of insects that can serve as vectors to transmit *T. cruzi*.
12. What are the critical issues that need to be addressed in regards to Chagas' disease?
13. In the chronic phase of Chagas' disease, at what point do symptoms like cardiomyopathy and megasyndrome develop?

5. Answers to Review Questions

1. False
2. D: 20-21 million
3. B: Trypanosoma cruzi
4. Reduviid insects or triatomines (i.e. *Triatoma infestans*)
5. Epimastigote, Trypomastigote, Amastigote
6. Digestive tract
7. The epimastigote form is recognized by the complement component of the immune system and is lysed by the membrane attack complex and thus cannot invade cells and grow.
8. It is not recognized by the complement system and so it is not lysed upon entry into the host and has the ability to invade host cells and replicate.
9. Cardiomyopathy – enlargement of the heart
10. Housing improvements, insecticide spraying = control of vector contact with humans.

11. True

12. Effective and sustained surveillance (vector control) and better drugs for treatment.

13. Usually decades after the original infection.

6. Discussion Questions

1. The human immune system is theoretically designed to clear any possible pathogen that we come in contact with. However, sometimes this does not happen. Is it because the hosts' immune system in not functioning properly? Is it because the pathogen has developed a mechanism for evading the host immune system? Or is it for both of these reasons, or something else? Think of this in the context of T. cruzi infection, especially regarding the different forms of the parasite present in chronically infected people.
2. Since Chagas' disease is really a disease of poverty, would eliminating poverty eliminate the disease? What else might have to be considered when trying to eliminate the spread of T. cruzi? How would you accomplish the elimination of Chagas' disease?
3. Vaccination has proven effective as a means of disease prevention. Do you think a vaccine could be developed for T. cruzi? What are some barriers to the development of a vaccine?
4. Why do you think the eye a common portal of entry for T. cruzi? What makes the environment in the eye beneficial for survival of the parasite?
5. Why are their so few drugs available to treat Chagas' disease? Why is it hard to find and develop a drug for treatment?

7. Answers to Discussion Questions

1. The infectious form of T. cruzi – trypomastigote – is resistant to complement, so even if this part of the host's immune system is functioning properly, the pathogen

has a mechanism for evading destruction. Also, because the pathogen can invade and replicate inside many different cell types, it has the ability to hide from other components of the immune system. On the other hand, individuals with immune system defects are more susceptible to infections. So the outcome of an acute infection is dependent not only on the pathogen, but also on the host's immune system. The outcome of the "war" that is fought between the pathogen and the immune system can end many different ways: sometimes the immune system wins (clearance of pathogen and recovery), sometimes the pathogen wins (death of the host), and sometimes it is a stalemate (persistent or chronic infection). The chronic form of Chagas' disease has many different manifestations – asymptomatic, cardiomyopathy, and megasyndrome, showing that the clinical manifestations of a persistent/chronic infection can vary widely. It is still unknown what determines the chronic symptoms that a patient presents. Pathogens co-evolve with their hosts, and Chagas' disease is a good example of how a chronic infection is favored because it is advantageous to the parasite, ensuring that it is maintained in the population.

2. The elimination of poverty in developing countries has proved promising for the control of disease spread. Improvements in housing, social and economical conditions have proved effective thus far. Elimination of poverty would go a long way to helping eliminate disease spread, but it would probably not completely eliminate it. The insect vector would still be present in the environment, and there are many hosts other than humans that can become infected and perpetuate the parasite. Thus, one important additional aspect to consider is control of human contact with the insect vector. This goes hand in hand with elimination of poverty to help control disease spread. If governmental programs could be implemented to effectively control the insect vector, this would help immensely. The elimination of Chagas' disease will involve political will and funding, in order to accomplish the different interventions necessary to control disease spread to humans.

3. Vaccine development will likely be difficult, because the serious symptoms of chronic Chagas' disease develop decades after the original infection. It would be very difficult to design a clinical trial to test the effectiveness of a vaccine. There is still a lot that is not known about the basic biology of T. cruzi, and this is a major barrier to the development of a vaccine. Also, to develop a vaccine is very time consuming and expensive. Most vaccine manufacturers are not likely to invest the time and money required for the development of a vaccine that will not generate enough money to recover their expenses. Considering that Chagas' disease affects almost

exclusively poor populations, funding from governmental or philanthropic organizations would be needed in order to develop and distribute a vaccine.

4. The eye is a common portal of entry for T. cruzi because it is an easy way to gain access to the host. Normally, contact of the feces of the insect with a break in the skin or mucosal membranes is necessary to allow entry of the parasite. This occurs most frequently in the eye because it is always exposed to the environment. The eye has some barriers for pathogens (tears, lysozyme, etc.) but these mechanisms are not always sufficient to stop T. cruzi. Another reason might be that people often rub their eyes with their hands, and this can facilitate contamination of the mucosa of the eye with insect feces.

5. Since T. cruzi is a eukaryote, in many ways similar to our own cells, is difficult to find unique metabolic pathways to target with drugs. A drug that interferes with a shared metabolic pathway would be toxic to humans as well as to the parasite. As we learn more about the biology of T. cruzi, opportunities for the development of more specific drugs will increase. Drug development is expensive and time consuming, so partnerships between industry, government and philanthropic organizations are also very important. The good news is that this is already happening.

8. Explain or Teach These Concepts to a Friend

1. Explain the life cycle of *T. cruzi*. Make sure to include the host and insect forms of the parasite. Be as detailed as possible. Also include why *T. cruzi* will probably never be eradicated from nature.
2. Explain the difference between the acute phase and chronic phase of Chagas' disease. Make sure to include when people are most likely to die, and why.
3. What has been done to control the spread of *T. cruzi*? How effective has it been, and what else might need to be done to effectively stop human infections?

9. Research the Literature on Your Own

1. What has been learned about Leishmania survival within the host cell since this seminar was given (April 2007)?
2. What has been learned about T. cruzi survival within the host cell since this seminar was given (April 2007)?
3. What other facts have we learned about cell biology because of the study of Trypanosoma and Leishmania species?
4. What else has been done using LIT1? Have homologues of this protein been found in other intracellular pathogens?
5. What other types of cellular processes is calcium signaling involved in? Is this a mechanism that is found only in mammals?
6. What else has been discovered about lysosomal pathways since this seminar was given? Have any other intracellular pathogens been described that also replicate within the lysosomal pathway or the endocytic pathway?