Nucleotide Metabolism and Human Disease

Note to instructors: Most of the sources cited at the bottom of the handout are websites that are no longer present or have changed their URLs. The following list of links are currently offered by the cited organizations:

Purine Research Society: http://www.purineresearchsociety.org/
Nucleotide Metabolism: http://themedicalbiochemistrypage.org/nucleotide-metabolism.html
Purine Metabolic Patients' Association: http://www.pumpa.org.uk/index.php

Red yeast to human disease: the unexpected consequences of genetic defects in nucleotide metabolism

Even before you took this course you probably knew that DNA was pretty darn important. You might predict (correctly) that if an organism couldn't make or obtain the components of DNA, that the organism would die. However, as you saw in the yeast studies, sometimes the effects of defects in making nucleotides are surprising. As expected, yeast that can't make adenine die unless they can get it from their environment. But their red color is less expected, although it makes sense when adenine metabolism is considered in more detail.

Metabolism is a word used to describe a collection of chemical reactions. Nucleotide metabolism, therefore, is the set of reactions involved in creating, using, or breaking down the components of nucleotides. Looking at the purine metabolism chart included in your lab manual, and realizing that this is just a portion of nucleotide metabolism (for example it doesn't include the making or use of pyrimidines), you can see that there are many possibilities for complexities. Nucleotide metabolism looks more like a web than a straight line. Thus, if there is a defect in a particular enzyme, the cell might not die because there may be other ways to make the product that the defective enzyme would usually make. But defects in nucleotide metabolism can still have dramatic consequences for an organism.

You have seen that yeast can exist with such defects, as long as they can obtain the missing product (e.g., adenine) from their environment. What of humans with genetic defects in nucleotide metabolism? Is this just some weird yeast thing or do humans with similar problems exist? If so, what are the consequences of those genetic alterations? Can studying nucleotide metabolism help humans live better lives?

Yes, there are humans with defects in nucleotide metabolism. The most common sort of nucleotide metabolic defect seen in humans is that of purine metabolism. There are at least 25 diseases in humans that are due to some problem in purine metabolism! A few more diseases are due to defects in pyrimidine metabolism. A few of these diseases are mentioned below.

Gout and Lesch-Nyhan Syndrome– When old nucleotides are broken down, the bases can be re-used to make new nucleotides. Any leftover purines that are not recycled are broken down into uric acid, an insoluble crystal that is excreted in urine (it's also the white stuff in bird poop). If one of the enzymes involved in recycling process is somewhat defective (the enzyme labeled 2.4.2.8 near the middle of the purine metabolism chart), this recycling process is not very efficient, and instead lots of purines are broken down into lots of uric acid because they cannot be reused. This excess insoluble uric acid cannot be cleared from the body and precipitates in the joints causing pain and inflammation known as gout. If the enzyme is completely defective, as in Lesch-Nylan syndrome, the symptoms of gout are overlaid by severe problems in the nervous system, leading to death before the age of 20.

Severe Combined Immunodeficiency (SCID) – This disease is often referred to as "bubble boy disease" as public awareness of the disease was raised by a made-for-TV movie starring a young John Travolta called The Boy in the Plastic Bubble (1976). A similar movie was made in 2001.

SCID is due to a defect in the breaking down of purines. The effects are complicated and reflect the web-like nature of nucleotide metabolism. If a single enzyme (labeled 3.5.4.4 on the metabolism chart) involved in this process is defective, certain purines build up. The recycling enzymes, which are normal in people with SCID, take these built-up purines and recycle them into dATP. This doesn't seem like a bad thing, does it? After all, you need dATP to make DNA. However, because the cell then has so much dATP the cell mistakenly "thinks" it has plenty of ALL the deoxyribonucleotides and disastrously shuts down synthesis of dTTP, dGTP, dCTP as well as dATP (this is due to feedback inhibition, which you will learn about in this course). This puts the cell in a pretty pickle, as now it can't make DNA because it doesn't have the T, G, or C deoxyribonucleotides. The cell then dies when it tries to reproduce because it can't make a copy of its DNA for the new cell. The cells most dramatically affected are those in the immune system as they reproduce frequently and have a very active recycling pathway. Since these cells die, people with this disease have very impaired immunity; they cannot resist infectious diseases and must live their short lives (the real bubble boy died at 12) in isolation from the environment (hence the term "bubble boy"). If these protective measures are not taken, the child dies in infancy.

Because the nature of this disease is well understood, some therapies are possible. Some children receive doses of the missing enzyme to help correct their problem. Some receive transfusions of healthy bone marrow immune cells from a donor (the real "bubble boy" had this treatment, but he died because there was the mononucleosis virus present in the cells he received). SCID has also been the target of gene therapy, in which the gene encoding the missing enzyme is given to the children, with some success in recent years. However, one of the recipients of the therapy developed leukemia, probably as a result of the therapy (the added DNA messed up some of the cell's DNA), so this is not without significant risk.

Autism – Some 25% of the autistic population is known to make excess purines. Exactly what the defect is that causes this and how it relates to the symptoms of autism (lack of social interaction and presence of certain repetitive behaviors) is unclear.

References:

1) Purine Research Society: http://www2.dgsys.com/~purine/
2) Nucleotide metabolism: http://www.indstate.edu/thcme/mwking/nucleotide-metabolism.html
3) The Purine Metabolic Patients Association: http://www.pumpa.co.uk/pages/research.htm

For recent news about gene therapy for SCID:

1) http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/G/GeneTherapy.html