Chapter 34

Resveratrol: A Real Anti-aging Product

The biological process of aging is a mystery. Many definitions are applied to and much controversy surrounds the discussion about aging, yet its true nature is still uncertain. A number of scientists believe that aging is not a biological process that you are subject to undergo throughout time; rather, they believe that aging is mainly multiple environmentally induced changes in the basic biological system. True, there are some genetic components, but only a few, because approximately 80% of the aging process seems to be self-induced. A major cause is overeating, followed by smoking, sunbathing, lack of exercise and psychological stress. Because there are many repair mechanisms in the body, it seems unlikely that there would also be a death gene or something that is designed to terminate life at a relatively early age. Of all the anti-aging methods proposed, and all the drugs and chemicals advertised, only one method appears to work, at least in mice, and that is dietary restriction.

One group of scientists working to understand aging mechanisms and age intervention discovered that a certain chemical, when taken orally, could provide similar benefits as offered by dietary restriction. [1, 2] Essentially, three groups of mice were studied for the effects of dietary restriction. One group was allowed unlimited food known as "ad lib;" a second group was given an ad lib diet plus a natural chemical from red wine; and a third group was put on a caloric-restriction diet. The results showed that the caloric-restriction group and the ad lib group with the natural chemical from red wine lived the same length of time and enjoyed a similar health benefit. The ad lib group all died early. The natural chemical from red wine used in this study was **resveratrol**, which is the topic of this chapter.

What is resveratrol?

Resveratrol is a plant compound, chemically known as 3,5,4’-trihydrostilbene, a member of the stilbene family, which is a group of compounds that is made up of two aromatic rings and is joined by a link known as a methylene bridge. (See **Figure 34-1**.) There are more than 30 stilbenes in the plant kingdom, but resveratrol is the parent molecule of a group of compounds known as viniferins[a], a family of phytoalexin polymers that prevents bacterial and fungal infections in plants. The phytoalexin are produced by the plant as a defense mechanism.

Although resveratrol is found in at least 72 plants, it is not found in many of the edible ones; peanuts and grapes seem to be the major edible sources. A weed that grows in Eastern Asia known as *Polygonum cuspidatum* is the richest natural source of resveratrol.

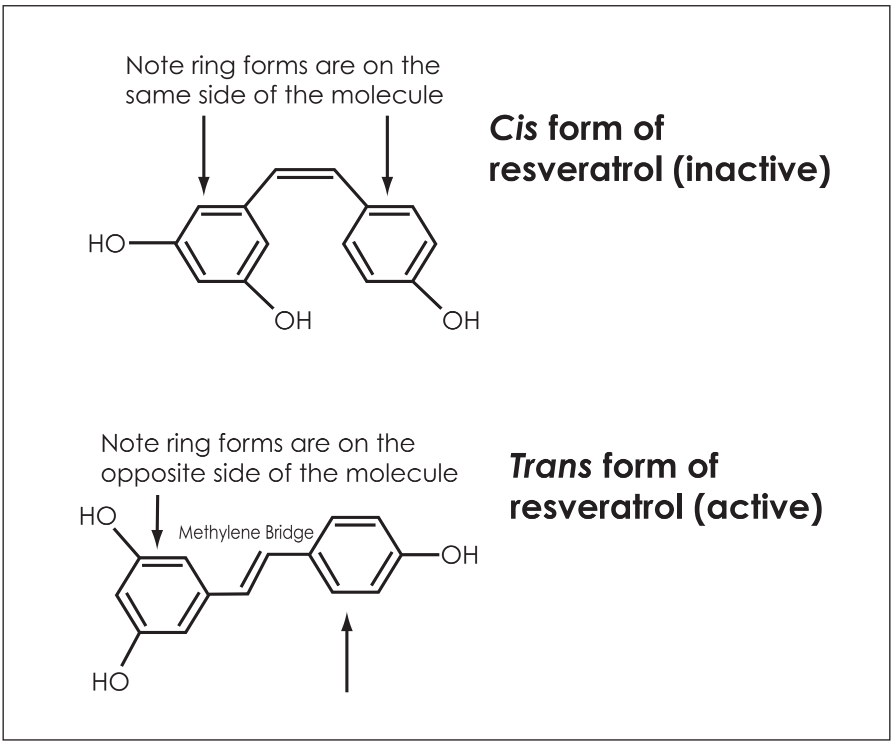

Figure 34-1. *The molecules of resveratrol—the* cis- *, or inactive, form of resveratrol (top); and the* trans-*, active, form of resveratrol (bottom).*

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[a] *Viniferins are complex molecules that develop in grape leaves and wood in response to fungal infections.*

Sirtuins and resveratrol

Much of the research into aging mechanisms centers on cell growth and the control of cell growth. One gene that has been studied extensively in lower life forms in this regard is silent information regulator 2 (Sir2) proteins, or **sirtuins**. They are enzymes characterized as deacetylases/mono-ADP-ribosyltransferases and are found in many organisms, ranging from bacteria to humans.

The first concept to understand is that sirtuins remove acetyl groups[b] from proteins. They do this in the presence of nicotinamide adenine dinucleotide (NAD+); that is how it gets its name as a NAD+-dependent deacetylases. Now it must do something with this acetyl group, so the sirtuins then take the acetyl group from the protein and add it to the ADP-ribose part of NAD+ to form adenosine diphosphate (O-acetyl-ADP), a lower energy form of the high energy form known as adenosine triphosphate (ATP), a major source of energy in biology. Here is the key phrase: energy-linked. When you see sirtuins and ADP, you know ATP—or energy—is not far behind. This is how it works.

This tells you that sirtuins are linked in some manner to the generation of ATP. That is the first key concept. The hydrolysis[c] of this protein, whatever it may be, yields three compounds: O-acetyl-ADP-ribose, the deacetylated substrate and nicotinamide. The dependence of sirtuins on NAD links their enzymatic activity to the energy state of the cell through the cellular NAD:NADH ratio[d]. You can see this reaction that shows the acetylation process. (See **Figure 34-2**.) Due to this relationship with energy, sirtuins have been associated in the regulation of aging, transcription, apoptosis and stress-resistance.

The regulation of many metabolic processes and cellular defense mechanisms could easily be the key to a possible lifespan-extending role for sirtuins in mammals. This reaction ties in with the histones and deacetylation and finally, resveratrol. Keep in mind that all this discussion relates to turning on a cell's metabolic mechanisms, as well as turning them off. It is very similar to a traffic light that has green for go, red for stop and yellow for caution.

A brief cell review

A cell consists of a membrane, cytoplasm, a nucleus and organelles, such as the mitochondria. Deoxyribonucleic acid (DNA) is the body's master template. Any time a protein—or any complex substance in the body—is made, DNA must open its two strands and expose the code for that substance. The

[b] *An acetyl group is a two carbon compound with formula CH3-COO. It is essentially vinegar.*

[c] *Hydrolysis is a chemical process in which a water molecule is removed from a protein.*

[d] *NAD:NADH is called a redox reaction because it shuttles protons and electrons back and forth.*

code is copied in a process called transcription, and the copy is sent to the reticuloendothelium, an organelle in the cytoplasm, which then translates the copied code into the substance or protein. So **transcription** and **translation** are the two key words in molecular biology. All of this is written about in many basic textbooks in biology. If you can remember the acts of transcription and translation, you have a grasp on biology. The DNA code can only be initiated by transcription.

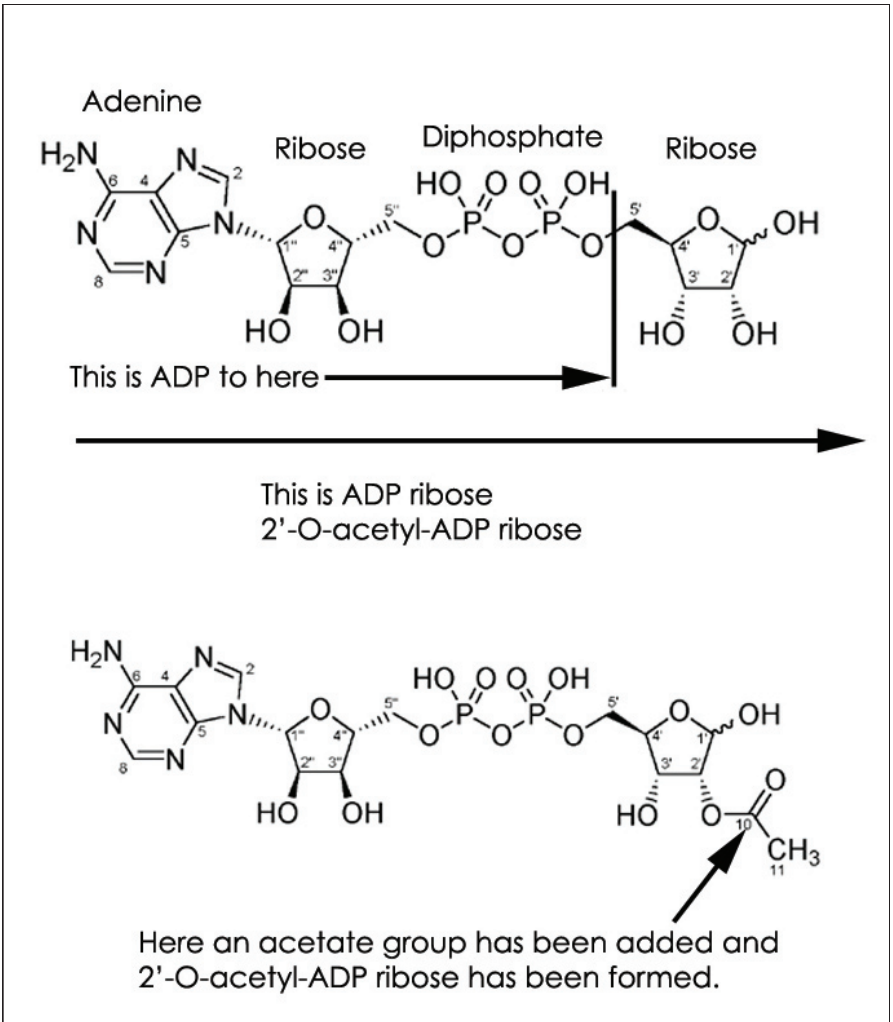

Figure 34-2. *The acetylation process*

Histones and deacetylation

This concept is critical to understanding resveratrol action. DNA[e], which is the genetic-containing molecule in every body cell, is a very large, very complex and very long molecule. In each cell, it is 1.8 m long when unwound. Think about that: A cell is only about 80–100 microns in diameter, while a strand of DNA is 1,800 mm, or 1,800,000 microns long. That is 18,000 times longer than the cell. Now, to get the DNA into the cell, it needs to be wound up to fit into a very tiny space. The cell uses tiny protein balls called **histones** to serve as the surface on which to wind the DNA. **Figure 34-3** shows a segment of DNA wrapped around some histones. Actually, they assemble to form one nucleosome core particle by wrapping 146 base pairs[f] of DNA around the protein spool in a spiral. These histones with DNA wrapped around them form a string of beads with some space between, called linker DNA. It looks much like a very long rosary and is called chromatin. (See **Figure 34-4**.) Before any message can be transmitted to the DNA, this giant molecule must open up, unwind and expose the code. If the DNA does not unwind, there can be no cellular action. Now here is where the deacetylation comes in.

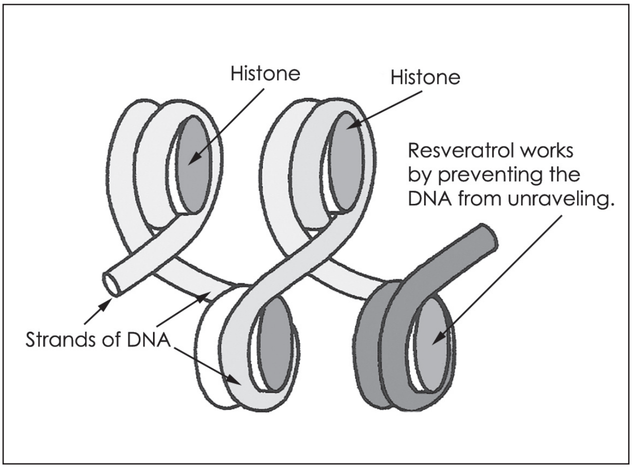

Figure 34-3. *Histones wrapped with DNA strands.*

Acetic acid can be added to a molecule under certain circumstances and this is called **acetylation**. If it is removed, this is called **deacetylation**. It is known that when DNA is active, the histones are acetylated; if they are deacetylated, they become less active. Following is a short explanation for this phenomenon.

Histones have positive ends due to amine groups present on their lysine and arginine amino acids. The positive charges help the amines to interact with and bind to the negatively charged phosphate groups on the DNA back.

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[e] *DNA is short for deoxyribonucleic acid, the protein that contains all the genetic material needed to develop a human from conception and maintain the body throughout its life.*

[f] *Bases in DNA are known as thymine, adenine, guanine and cytosine. A base pair consists of two of these bases chemically bonded across from each other in a strand of DNA. Cytosine can only bind to guanine and thymine can only bind go adenine, and vice versa.*