The Molecular Perspective: Estrogen Sulfotransferase

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LEARNING OBJECTIVE
After completing this course, the reader will be able to:
1. Discuss estrogen sulfonation and its potential role in cancer therapy.

Many hormones, drugs, and toxins are small, carbon-rich molecules and are thus insoluble in water. This poses a physiological problem: how do you move these molecules from place to place since the major pipeline of transport is the watery circulatory system? This applies to molecules such as steroid hormones, which must be delivered from glands to target tissues, and toxins, which need to be solubilized so they can be excreted.

One method to make a molecule more soluble is to add a charged chemical group to it. Sulfotransferases use this approach. They attach a negatively-charged sulfonate group to convenient hydroxyl or amine groups on insoluble molecules. Sulfotransferases, like many other enzymes that modify and detoxify small, carbon-rich molecules, tend to be rather non-specific, adding sulfate groups to many different molecules of approximately the same shape and size. Despite this broad specificity, cells make dozens of different sulfotransferases, each acting on a slightly different collection of molecules.

Sulfonation can have widely different effects, depending on the molecule. In the case of the painkiller acetaminophen, adding a sulfate detoxifies the molecule, making it easier to excrete. In the case of minoxidil, which is used to promote hair growth, the addition of a sulfate activates the molecule as a drug. In the case of some polycyclic aromatic compounds, the addition of a sulfate turns molecules into powerful mutagens that attack DNA. And with estrogen (Fig. 1), the sulfate provides a ready method to control the level and activity of the hormone.

Sulfonation of estrogen generally inactivates the hormone by making it more soluble. However, sulfonated steroids have a long half-life, so they can act as ready hormone storehouses when needed. Because of this, estrone sulfates

Figure 1. PAPS, a doubly phosphorylated adenosine nucleoside, is the cofactor that donates sulfate groups in the sulfotransferase reaction. Sulfonated and active estradiol molecules are shown on the right.
are common in the blood. When needed, they are readily converted to active estrogens by removal of the sulfate by a sulfatase enzyme, such as that shown in Figure 2. This balance of sulfonated and active forms is controlled by two antagonistic enzymes: sulfotransferases adding sulfonyl groups and sulfatases removing them.

The sulfotransferases and sulfatases that act on estrogen are attractive targets for cancer therapy since some breast cancer cells require a steady supply of estrogen for growth. In particular, sulfatases help maintain high levels of active estrogen, and thus drugs that attack this enzyme could be effective in controlling cancer growth.

**Disclosure of Potential Conflicts of Interest**
The author indicates no potential conflicts of interest.

**Further Reading**


Figure 2. Estrogen sulfotransferase is a small soluble enzyme found in cytoplasm. It uses a specific cofactor, PAPS, to transfer a sulfonate group to estrogen and other steroids. Estrone sulfatase is found in the endoplasmic reticulum, where it performs the opposite job of removing sulfate groups. The large arm anchors the enzyme into membranes and places the active site near the membrane surface. The arrow points to an opening that leads to the active site deep inside the enzyme. Atomic structures were taken from entries 1aqu and 1p49 at the Protein Data Bank (http://www.pdb.org).