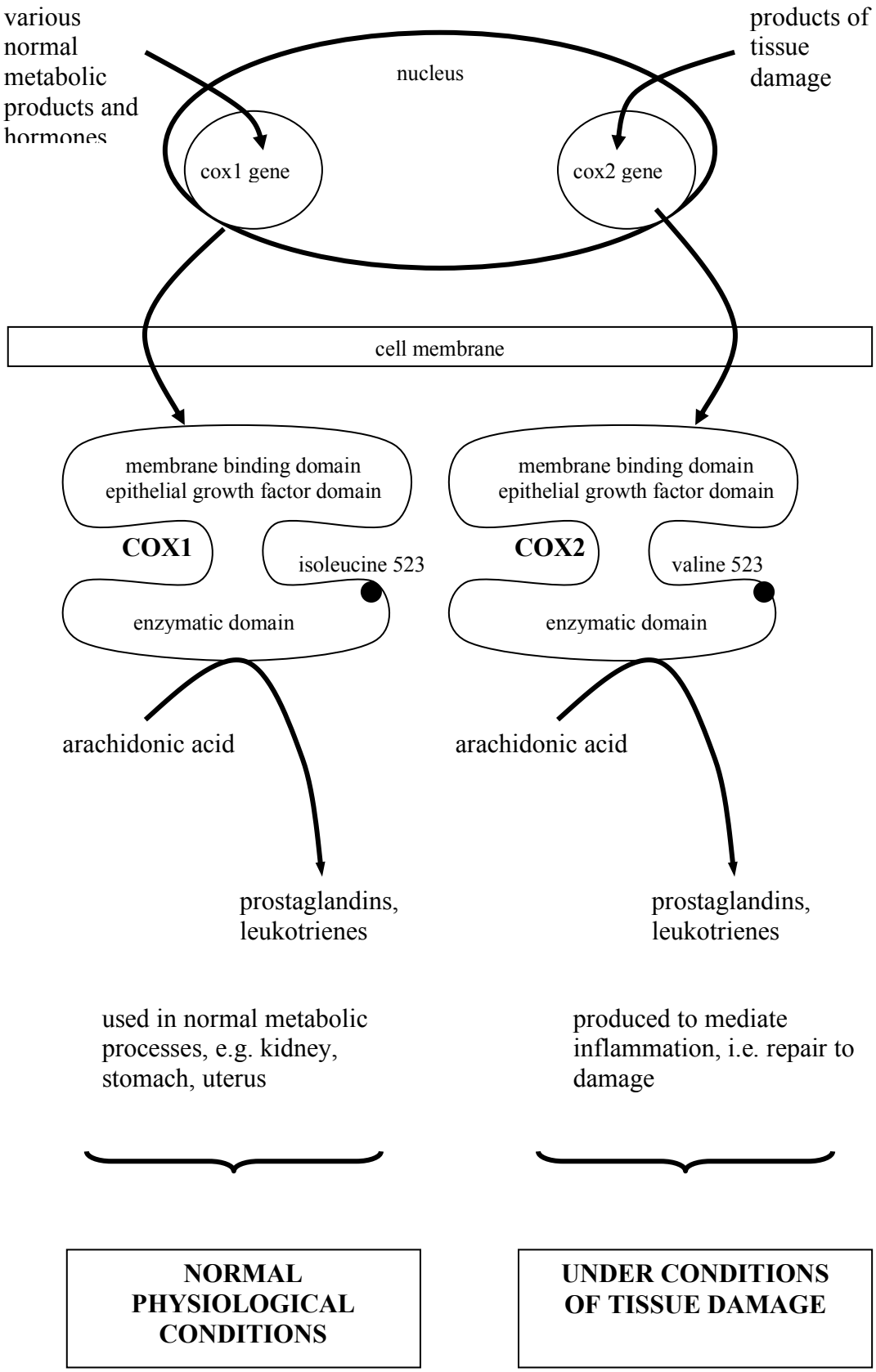

Dear Peter

The COX story goes like this (see figure).

There is an enzyme called cyclo-oxygenase. This enzyme operates on arachidonic acid to produce prostaglandins and leukotrienes (see accompanying notes).

COX has a structure such that one end consists of a membrane binding domain together with an epithelial growth factor domain. [We are not concerned with these domains, save to appreciate that the enzyme is bound to cell membranes]. The other end is the active, enzymatic end, which acts on arachidonic acid. [This is the end in which we are interested.]

Notwithstanding various intermediate steps (involving ribosomes and RNA), COX is generated by genes in the nucleus of the cell.

COX can exist in two forms: COX1 and COX 2. They differ from one another only with respect to the amino acid at site 523. In COX1 the acid is isoleucine. In COX2 it is valine.

Each isoenzyme is produced by a different gene. Each gene is activated by different factors.

The production of COX1 is triggered by various, normal metabolites and hormones. The COX that is produced produces prostaglandins and leukotrienes that the body wants to have, and likes to have, in order to mediate various normal physiological processes, largely involving blood flow through tissues, particularly in the stomach and kidney (see accompanying notes).

COX1 is being produced all the time.

The production of COX2 is triggered by tissue damage. The prostaglandins that COX2 produces are used in the inflammatory response to the tissue damage, and are designed to promote repair, i.e. inflammation is a good process.

Picture it this way. Normal COX, in the form of COX1, cannot produce enough PGs and LTs to mediate inflammation. When you need extra PGs and LTs for repair activities, COX2 kicks in.

There is no difference in what COX1 or COX2 produce. They both do the same thing to arachidonic acid.

The difference lies in the genes that produce them and the factors that trigger those genes.

Now, when you develop a drug that blocks COX, it acts on the enzymatic domain. NSAIDs are such drugs.

The original NSAIDs operated on sites in the COX molecule that were identical in both forms. So, they blocked COX1 and COX2. Because of this, they would block not only the inflammatory effects of COX2 but also the normal physiological effects of COX1. Consequently, these NSAIDs had side effects, on the kidney and stomach.

This occurs because, while you administer NSAIDs hoping that they will get to the inflamed tissue, where they will block COX2, the drug also gets to normal tissues, where it blocks COX1.

COX2-inhibitors are an NSAID that take advantage of the one amino acid difference between COX1 and COX2. They bind to a site on COX2 that is not present, or not accessible, in the COX1 molecule. Consequently, these agents can block the inflammatory effects of COX2, but have no influence on the normal physiological effects of COX1. You administer them in the hope that they will get to the inflamed tissues where they will block COX2. If any of the drug also circulates to normal tissues in which COX1 is present, they will have no effect on COX1. Consequently, they will not have the side effects on these tissues (or so the theory goes).

I think that the basis for you confusion is that you overlooked the fact that COX1 is an enzyme that is present normally, all the time, whose role is to produce mediators of normal metabolic processes.

COX2 is like a regiment in reserve, held out of action until it is urgently need to repair tissue damage.

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