Cisplatin provides a perfect example of how small changes in molecular structure can lead to profound differences in biological activity. It is a tiny molecule, composed of a platinum ion surrounded by four ligands arranged in a square. If you choose two amines and two chlorides as ligands, there are two ways to arrange them around the platinum ion. In cisplatin (Fig. 1), the chlorides are next to each other, and treatment with the compound can cure testicular cancer. If the chlorides are arranged opposite one another, however, the compound has no activity.

The reason for this difference becomes apparent when you look at the cellular target of cisplatin. Inside a cell, cisplatin loses its two chloride ions, creating a reactive species that forms bonds with DNA bases. Because of the cis geometry of these bonds, cisplatin easily forms crosslinks between bases, as shown in Figure 2. Most of these crosslinks are formed at sites where guanine and adenine are next to each other in the same strand, but in some cases, cisplatin can form links between the two strands. As you might imagine, these crosslinks cause severe problems when the cell attempts to read or replicate its DNA.

**Figure 1.** Cisplatin and its relatives are composed of a doubly charged platinum ion (in grey) surrounded by four ligands. In this illustration, the ligands on the right (chloride in cisplatin and carboxylate compounds in the others) are the leaving groups, allowing the platinum ion to form bonds with DNA bases. The amine ligands on the left form stronger interactions with the platinum ion and will remain bonded when the drug forms crosslinks with DNA.
The chloride ions in cisplatin are particularly important in its action as a drug. They are relatively stable when the drug is outside the cell, where the chloride concentration is normally high. But when the drug gets inside the cell and the chloride concentration drops, cisplatin loses its two chlorides, and they are replaced by water molecules. These water molecules are loosely bound and fall off easily, allowing the platinum to attack other molecules, such as DNA. In spite of this simple targeting mechanism, 9 out of 10 cisplatin molecules still get stuck on plasma proteins before they reach the nucleus.

Unfortunately, cisplatin has significant limitations. Treatment with cisplatin causes severe side effects, and cisplatin is effective for only a specific range of cancers. Many crosslinking platinum compounds have been tested in an attempt to correct these disadvantages. Two successful modifications are shown in Figure 1. In carboplatin, the chloride groups have been changed, resulting in better delivery to cells and fewer side effects. In oxaliplatin, the amino groups have been changed as well, forming a bulkier crosslink that is effective on a different range of cells.

The detailed mechanism by which cisplatin kills cancer cells is still being actively studied, but apoptosis appears to play a central role. Resistance is a significant problem with cisplatin treatment: cells use all the mechanisms at their disposal to fight poisoning by cisplatin. They reduce the amount of cisplatin reaching the nucleus, perhaps through the use of the mechanisms involved in the maintenance of copper levels. Once the platinum is bound to DNA, cells use their powerful nucleotide excision repair system to fix the problems. Testicular cancers appear to be particularly sensitive to cisplatin treatment because they are not as efficient in their repair mechanisms. Cancer cells also modify the proteins that sense damage and commit the cell to apoptosis, allowing platinated cells to bypass their normal checks and balances.

Further Reading

