TAXANES - MECHANISM OF ACTION

The taxanes are mitotic inhibitors, meaning that they inhibit tumors primarily by preventing cells from entering*mitosis*, a process of cell division. The taxanes accomplish this by inhibiting microtubule polymerization. In addition, taxanes appear to stimulate *apoptosis*, or programmed cell death, which is often inhibited in cancer cells.

Microtubule polymerization

Microtubules[1] are tube-like structures within the cell, made up of tubulin heterodimers (molecules of tubulin, a protein, coupled with a partner molecule). Microtubules act as a skeleton, giving the cell its shape and positioning its internal organelles. In other instances, microtubules act as a transport network along which proteins and other molecules are ferried to the structures that need them. And, they play an essential role in cell division, physically separating the chromosomes for replication and carrying out the physical division of the cell (Desai and Mitchison 1997, p. 84). These microtubule functions are carried out through a dynamic recycling process in which the microtubules are lengthened, or *polymerized*, and shortened, or *depolymerized*, as needed. Unlike anthracyclines, which interfere directly with the transcription of DNA in the cell nucleus, taxanes work by disrupting microtubule polymerization, in turn preventing the cell from entering mitosis. Microtubules are naturally unstable, and grow or contract from the unstable bonds at their ends. Taxanes artificially stabilize the dynamic end bonds, essentially freezing disassembly, and in turn bring mitotic cell division to a halt. This inhibition of microtubule depolymerization is credited with causing

one of the more serious side effects of the taxanes, sensory neuropathy, or the destruction of sensory nerves (Ochs 2004, p. 294).

Apoptosis

As well as inhibiting cell division, the taxanes promote apoptosis[2]. This result may be a secondary effect of causing microtubule accumulation, or it may be caused directly by phosphorylation (chemically switching off) of a protein that blocks apoptosis in cancer cells. (E.g., Kovar et al. 2009; Sorger et al. 1997). Studies of novel taxanes confirm this effect (Yvon et al. 1999).

Footnotes:

1. Microtubules are tiny, tube-shaped molecules used within cells for structural support (like a skeleton), to expand or contract the cell (like muscles), or to transport chemicals between cell organs (like conveyor belts). Microtubules are constantly being reshaped through lengthening (*polymerization*) and shortening (*depolymerization*). Microtubules are essential to cell division, where they are used to physically divide and replicate the cell's DNA. Anti-cancer therapies, such as the taxanes, target the polymerization and depolymerization processes, seeking to freeze the microtubules within a cell, preventing normal cell processes and especially cell division.

2. Apoptosis, also known as programmed cell death, is a genetically determined series of steps by which a cell disintegrates. It is called "programmed" because the process is triggered by any of a predetermined sequence of events, including natural aging or the

accumulation of damage to the cell's nuclear DNA. It is an orderly process that prevents the release of harmful substances from the disintegrating cell. Apoptosis is one of the body's primary defenses against cancer, and in cancer cells natural apoptosis is often inhibited. Cancer therapies, including chemotherapy, seek to trigger or restore apoptosis as one means of combating cancer cells.

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