Drug Development Update: MEK Inhibitors

Growth factor receptors are well-known targets for cancer drugs like Tarceva (erlotinib), Tykerb (lapatinib), and Avastin (bevacizumab), among others. These receptors activate cell growth by initiating a chain of events that results in progression of the cell cycle which leads to cell division. You have probably heard about the growth factor receptors EGFR, HER2, and perhaps VEGFR. One of the limitations of targeting these receptors is that many of them share the same intracellular pathway to activate cell growth. When just one growth factor receptor is inhibited with a targeted therapy, other receptors can still activate the same downstream growth pathway.

To combat this, scientists are currently developing drugs that target these growth pathways further downstream than the growth factor receptors. The most common signaling cascade for cancer cell growth involves growth factor receptors activating a protein called Ras, which then activates Raf, which then activates MAPK/ERK kinase (MEK), which then activates ERK. ERK then directly activates proteins called transcription factors (namely Myc, Elk1, Fos, and Ets) that bind to DNA and tell the cell to make proteins from certain genes that drive cell division forward, such as Cyclin D. ERK also indirectly activates proteins called RSK that speed up the protein-making machinery inside a cell, allowing the cell division to move ever faster.

Because this Ras/Raf/MEK/ERK pathway can be activated by multiple growth factor receptors, promising emerging targets in the treatment of cancer are the MEK proteins. Since many growth signals converge ultimately with the activation of ERK, deactivating MEK should stop ERK from functioning in the cell. Unfortunately, two of the first MEK inhibitors were discontinued after disappointing phase II clinical trials. This was most likely due to problems with the specific drug design, however, and newer second-generation MEK inhibitors such as selumetinib demonstrate much better pharmacokinetics.

One other problem with the first generation MEK inhibitors was the design of the clinical trials. New evidence is emerging that suggests certain patients, whose tumors are known to be dependent on the Ras/Raf/MEK/ERK pathway for cell growth, will likely benefit more from these inhibitors than other patients. For example, preclinical data suggests that patients whose tumors have activating B-Raf mutations respond very well to MEK inhibitors since they are addicted to this pathway for growth (as detailed in a review of MEK inhibitors). Importantly, MEK inhibitors are mainly cytostatic drugs, meaning they stop tumor cells from growing, but they do not actually kill tumor cells. Clinical trials with MEK inhibitors may also be more successful when MEK inhibitors are combined with standard platinum-containing chemotherapies since these platinum-based chemotherapies are cytotoxic and will kill the tumor cells.

Finally, there are also encouraging preclinical data supporting combinations of MEK inhibitors with other inhibitors that specifically target the Ras/Raf/MEK/ERK pathway. MEK inhibitors are
being investigated in the preclinical setting for concurrent use with growth factor receptor inhibitors like erlotinib. Additionally, a biologic phenomenon called negative feedback exists, whereby ERK actually drives proteins that turn off the Ras/Raf/MEK/ERK pathway upstream of ERK, at Ras and Raf. This happens in normal cells as part of the tight controls on cell cycle division. But in cancer, **treating a cell with a MEK inhibitor may activate Ras and Raf by removing the inhibitory proteins that ERK usually triggers.** Adding a Raf inhibitor to treatment regimens containing MEK inhibitors may help combat the effects of negative feedback on this pathway when MEK inhibitors are used alone.