

2009 Berkeley Ras-MAPK Pathway conference review

The Ras/MAPK pathway conference was held at a hotel at the Berkeley Marina on August 1st and 2nd. It consisted of presentations from researchers and medical doctors who have interest in the Ras/MAPK pathway due to its link to cancer and 6 genetic syndromes – CFC, Noonan, Costello, Neurofibromatosis Type I, LEOPARD, and Legius.

The Ras/MAPK pathway is a message signaling pathway that used by the body to pass a message from outside the cell to the cell nucleus. The types of messages that are relayed through this pathway include cell differentiation (become a liver cell, a muscle cell, a neuron, a skin cell, etc.), apoptosis (cell death), and cell division. This pathway is complex, making it difficult to describe. A simple explanation would be that it uses a series of proteins to pass the messages described in the same way a bucket brigade works. The proteins are formed from the pattern that DNA provides. The proteins involved in the bucket brigade come from different genes. When one of these genes has a mutation, it causes problems and determines which syndrome applies – the CFC-causing genes are B-Raf, MEK1 and MEK2. A new term being used by many of the researchers to refer to the collection of syndromes on the pathway is RASopathies

Keep in mind that there is a lot of overlap of symptoms between the syndromes. This is to be expected because the genes for the different syndromes are on the same pathway. At the same time, symptoms can vary greatly even among those with the same mutation on the same gene. A very interesting note that came out of the CFC conference presentations was presented by Dr. Grace Yoon, a geneticist from Toronto. She showed the cognitive function of three different individuals with the same mutation (Q257R) on the B-Raf gene. One had a mild mental disability, one was severely affected, and a third had a profound mental disability. Each person has 30,000 genes, all expressed a little different and all affecting how our other genes are expressed. This is what makes each of us unique in the world.

Several of the researchers who presented spoke about the drugs that have been developed to treat cancers that are caused by mutations on the pathway. 70% of all Melanoma skin cancers are caused by mutations on the B-Raf gene, with a high majority of the mutations being the “V600E” mutation (this describes the gene location where the mutation occurs). If a skin cell develops a B-Raf mutation, the Ras/MAPK pathway becomes activated independent of the signals it receives from the body. It continually divides due to the activation, causing cancer. There is a drug called Sorafenib that was developed by Nexavar and Bayer that targets the V600E mutation. The drug is a molecule that was designed to bind with the molecular structure of B-Raf so that the message being passed by the above-mentioned “bucket brigade” is stopped. This shuts down the pathway, thereby preventing cancer growth. This drug worked very well in a test-tube, but not so well in clinical trials. It is thought that the pathway has feedback loops that overcome the blocking of the message to keep the pathway activated. Kidney and Liver cancer patients apparently have very few treatment options, so it has been approved to treat those two cancers.

Another researcher spoke about a class of drugs called MEK inhibitors. These drugs work in the same way as B-Raf inhibitors (blocking the bucket brigade by creating a molecule that binds with the molecular structure of the target protein), except that they target the MEK gene. Right now there are about 10 companies working on MEK inhibitors. Some of them have shown great promise in treating cancers caused by pathway mutations. One drawback that is being found is that tumors start to grow again if the patient stops taking the drug.

How might these classes of drugs help our kids? In the test tube, most of the mutations our kids have cause the pathway to become activated. So if the message can be blocked, the pathway is not activated and some of the symptoms in our kids might go away. The only way to determine if the drugs will be effective is through clinical trials. These take time and money. They also require willing patients. CFC Syndrome has a very small cohort of patients. If all of the Rasopathy groups stick together, researchers will have access to a larger group of participants willing to participate in clinical trials.

There was quite a bit of interest in modeling various pathway mutations in mice and zebrafish. One researcher tried introducing the V600E cancer causing mutation in knock-in mice, but the embryos constantly died, suggesting that “sustained activation of the [pathway] is incompatible with survival. There was quite a bit of work done on CFC mutations in zebrafish. Researchers introduced B-Raf and MEK mutations in zebrafish and observed their development. Their development was significantly altered. In the next step, they used “chemical inhibitors” of the pathway when the zebrafish embryos were developing, and found that their development was near-normal. Their conclusion was that “treatment with a MEK inhibitor can restore the normal early development of the embryo, without the additional, unwanted developmental effects of the drug.”

One more fascinating bit of research was observed with Neurofibromatosis Type I knock-in mice. These mice had learning disabilities and attention deficits that were due to the NF1 genetic mutation. To quote from the abstract: “Recently, we discovered that statins, at concentrations ineffective in controls, can reverse their spatial learning and attention impairments. Strikingly, recently completed pilot clinical trials...uncovered suggestive evidence that statins may also be able to reverse cognitive deficits in children with NF1. This is an exciting discovery with potential to help our kids cognitive difficulties. It was noted by Dr. Grace Yoon, that statin drugs given at an early age can negatively affect myelination. Myelin is a material that forms a layer, the Myelin sheath, around the parts of our nerves and is essential for the proper functioning of the nervous system, especially coordination. So more research is needed before we put our kids on statin drugs.

It was personally exciting for me to see so much research into the Ras/MAPK pathway, specifically relating to the Rasopathies. I believe it will result in treatments that will help our kids, although it will probably take 3-5 years. I think it is imperative for the syndrome groups to work together in some form so that researchers have enough participants for their studies and so more funding dollars will be directed our way. Many thanks to Dr. Rauen and her group for organizing this scientific meeting of the minds.