

Genetics and pathogenesis of kidney angiomyolipoma: Role of MITF and other TFs

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Dr Kwiatkowski's greatest research achievement has been the discovery of the TSC1 gene, one of the two genes that cause TSC when mutated, published in the journal Science in 1997. This discovery and work done in the fruit fly, *Drosophila*, led to the first hints about the function of the TSC1 and TSC2 protein products. We now know that the TSC1/TSC2 protein complex has a critical role in regulating the activation of a master enzyme called mTOR, which acts in a signalling pathway that controls cell growth. This critical pathogenic insight led to the discovery of a new use for an old drug, Rapamycin (sirolimus), which works to block mTOR (mammalian Target Of Rapamycin). A series of randomised and other clinical trials have led to approval of rapamycin or a related drug everolimus for the treatment of tumours that occur in people with TSC. More recent studies both by Dr Kwiatkowski's lab and others have described the importance of mTOR signaling in a variety of cancers. Furthermore, a variety of common cancers have mutations in either TSC1 or TSC2, and this appears to predict response to treatment with mTOR inhibitors.

Renal or kidney angiomyolipoma (AML) is a slow growing benign kidney tumour, which is characterised by the presence of mature or immature fat tissue, thick-walled blood vessels, and smooth muscles. They are often seen in people with TSC. Although benign, they can become cancerous in very rare cases.

Kidney AML tumours are treated either with rapamycin and other rapalog inhibitors or require surgical intervention and transplantation. Prolonged treatment of these tumours is necessary, since they regrow after treatment is discontinued. So far, we have learned a great deal about both the molecular basis and clinical aspects of AMLs. However, the cell of origin and the role of driver events beyond genetic changes in TSC2 and TSC1 in kidney AML development are unknown. Dr Kwiatkowski and his team hypothesised that epigenetic (how our behaviours and environment can cause changes that affect the way our genes work) and transcriptional events (process of converting DNA into RNA) have a critical role in kidney AML tumour growth and progression and studied the gene expression profile and chromatin organisation (complex of DNA and proteins that form chromosomes) of these tumours

During his presentation at the international TSC research conference, Dr Kwiatkowski shared his findings about a specific transcription factor called MITF or Microphthalmia-associated transcription factor. A transcription factor is a protein that binds to DNA and controls the which genes are switched on to make proteins.

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MITF is found to be highly expressed in kidney AMLs. It works with other transcription factors - TFE3, TFEB and TFEC to drive tumour growth. Using highly sensitive techniques like RNA-seq (which can detect expression of hundreds of genes in a single assay) and ChIPseq (which can identify which part of gene is open and ready for transcription factors to bind and turn them on), Dr Kwiatkowski's team compared tissue samples from AML's with normal tissues.

Take home message from the presentation:

- The study has confirmed that MITF is expressed in all TSC tumour types with highest expression in AMLs
- It is likely that high expression of these transcription factors turns further genes on and therefore contributes to tumour growth
- MITF also controls its own turn-on and turn-off activity indicating it is a “master transcription factor”
- Other master transcription factors for AMLs are yet to be defined

In conclusion, Dr Kwiatkowski's team has identified unique chromatin signatures, and several highly expressed transcription factors which likely are essential for AML development, enabling potential novel treatment strategies.