Could a Protist help us understand cancer?

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Presenters

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Tetrahymena thermophila appear to use homologs of the proto-oncogenes k-Ras and Raf-1 to signal for cell division, which may make them an excellent model system for testing drugs used to some cancers.

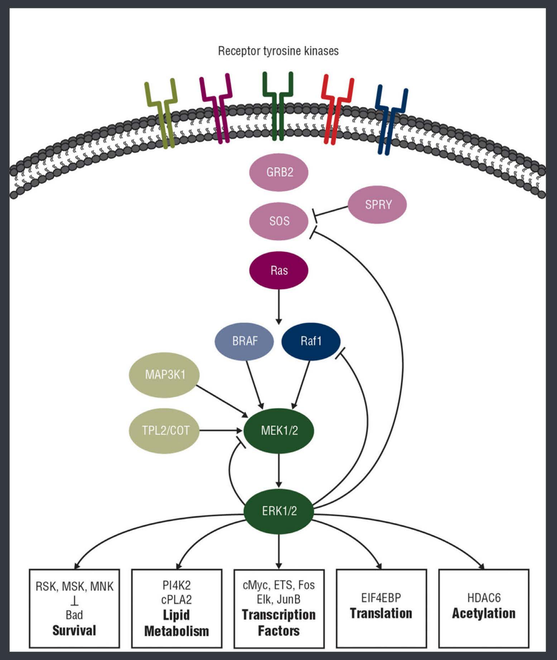

Figure 1. RTK signaling through Ras and Raf1 in mammalian cells. From esmo.com

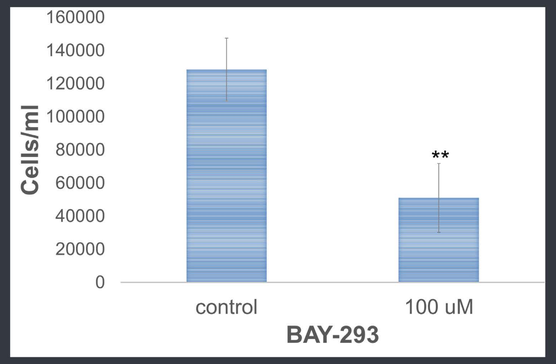

Figure 2. The Ras-Raf uncoupler, BAY-293, significantly inhibits cell division in *Tetrahymena thermophila* (p< 0.001).

Figure 3. BLAST alignment of human k-Ras with the*Tetrahymena* proteome reveals small G-proteins which are very similar to k-Ras.

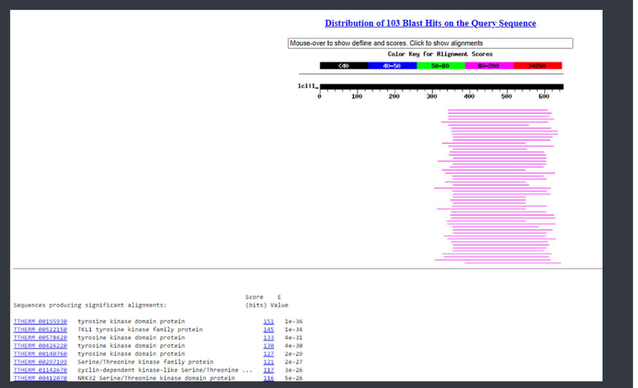

Figure 4. BLAST alignment of human Raf-1 with the *Tetrahymena* proteome reveals multiple tyrosine kinases and serine/threonine kinases which are highly similar to Raf-1 (a serine/threonine kinase).

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Abstract

Cancer is a deadly disease which affects millions of people globally. Cancer ultimately arises from dysregulation of growth pathways, leading to loss of cell cycle control and tumor formation. Cancer cells maintain constant cell division, evade immune detection, ignore signals for apoptosis, and may acquire the ability to degrade the extracellular matrix and metastasize.

Tetrahymena thermophila are free-living (non-parasitic) ciliated unicellular eukaryotes belonging to Kingdom Protista. They are often used as a model system because they are relatively inexpensive and easy to culture and maintain. In addition, it is relatively simple to grow and harvest large numbers of cells for biochemical applications such as protein, DNA, or RNA purification. Because of their adaptability as a model system, we asked whether whether *Tetrahymena* possessed two common pathways often dysregulated in cancer; the Wnt signaling pathway and the Ras signaling pathway. In order to test our hypothesis, we used the *Tetrahymena* genome database to search for homologs of Wnt, Ras, and Raf. In addition, we used a Wnt agonist and an antagonist of Ras/Raf inhibition to determine whether the mitotic rate would be affected. While the Wnt agonist had no significant affect on mitosis, the Ras/Raf inhibitor significantly decreased mitotic rate in this organism. We also found homologs of Ras and Raf in the *Tetrahymena* genome database. Further studies are needed in order to obtain an accurate dose-response curve with the Ras/Raf inhibitor, BAY-293.

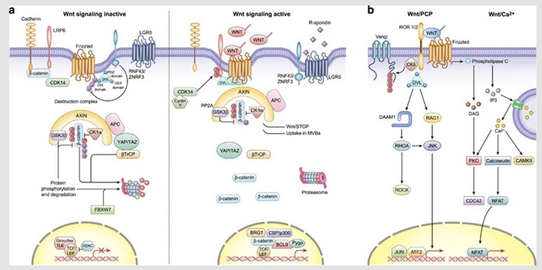
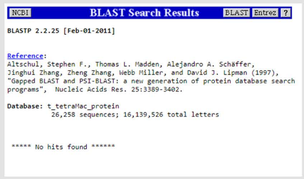


Figure 5. Wnt signaling in mammalian cells. From https://www.nature.com/articles/onc2016304/figures/1section



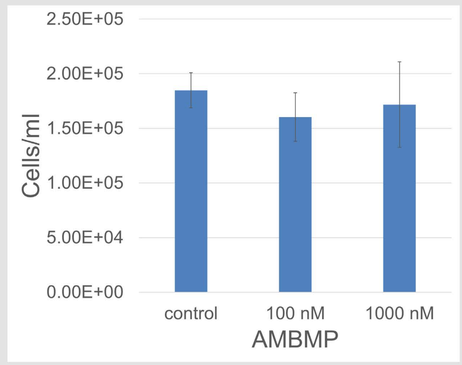


Figure 6. The Wnt agonist, AMBMP-HCl has no significant impact upon cell division in *Tetrahymena thermophila* (p=0.58, 0.81 for 100 and 1000 nM respectively). A BLAST alignment between Wnt-1 and the *Tetrahymena* proteome showed “no hits found” (pictured left).

Conclusions

- *Tetrahymena* appear to have homologs of Raf-1 and k-Ras, making them a good model system in which to study these proto-oncogenes.
- Ras/Raf communication appears to be necessary for cell division in *Tetrahymena.*
- The Ras-Raf uncoupler BAY-293 may be useful in stopping mitosis in cells where Ras is no longer regulated.
- *Tetrahymena* do not appear to have a homolog of Wnt and are unlikely to be good models for studying defects in this signaling pathway.
- Further studies are needed in order to obtain an accurate dose-response curve for BAY-293 and to determine whether MAP kinases are involved in this pathway.