A Rationale for the 'Design' of the MAP Kinase Pathway

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ABSTRACT

The MAP Kinase (MAPK) pathway [1] is a three-component cascade involved in a variety of cellular responses, ranging from stress-response, growth, differentiation and many other processes. What is remarkable about this system is that it is highly conserved throughout the entire eukaryotic kingdom. A variety of suggestions have been put forward to explain the function of MAPK, for example, that the MAPK operates as a high gain signal amplifier, or as a device which can act as a boolean switch. However a number of puzzles remain, why for example is the MAP Kinase pathway consistently made from three cascade steps? A second puzzle is that although three consecutive steps should able the pathway to generate very high gain, experimental evidence does not support this conjecture. This begs the question why employ three layers, when fewer could easily generate the observed modest amplification response?

In this poster I would like to suggest a novel explanation for the 'design' of the MAP Kinase pathway. In particular I would like to suggest that the MAP Kinase pathway is operating as a traditional op-amp device, that is a linear transducer. The MAPK pathway has a number of distinct features which enables it to act as an operational amplifier (or op-amp) device, these include:

1. The intrinsic high gain originating from three consecutive cascade steps

2. A negative feedback from the last stage to the first stage.

These arrangements enable the MAPK pathway to generate a remarkable degree of linearity between the input and output response over a wide range of input. This poster will describe various simulation studies and experimental data to show how a high gain cascade, coupled with a negative feedback loop, can generate behaviour than is indistinguishable from modern man-made op-amp devices.

REFERENCES

[1] Widmann, C., Gibson, S., Jarpe, M.B, and Johnson, G.L. Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. Physiol. Rev., 79, 143-180, 1999.