Exploring the combinatorial fitness landscape of co-evolving human and viral proteins

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Summary

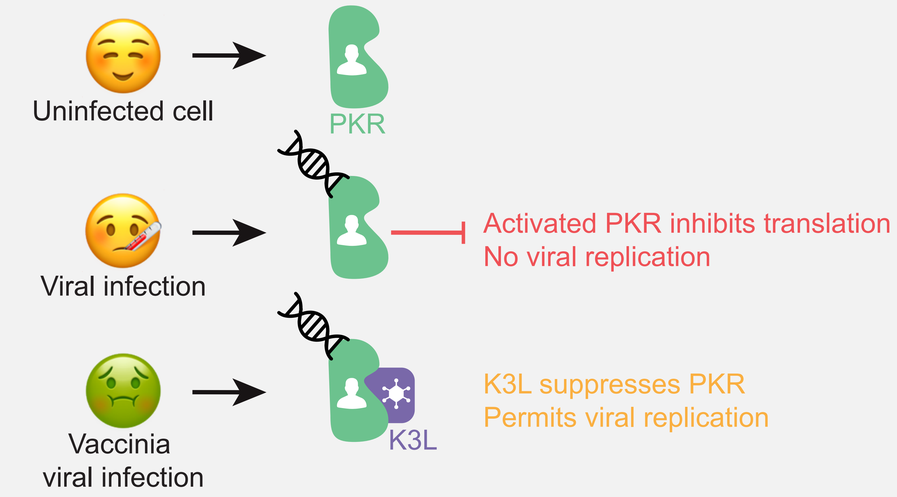
We are using deep mutational scanning to explore the evolutionary arms race between human PKR and poxvirus K3L.

We hypothesize that PKR may adopt a wider array of variants to escape K3L while K3L has limited variant options to improve affinity to PKR.

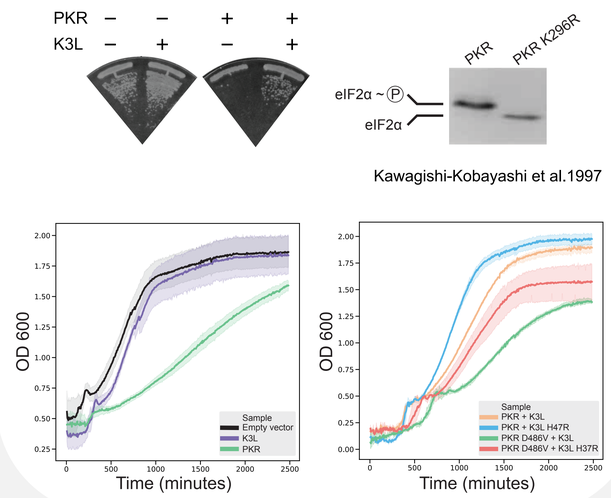
We are developing a method to generate single residue variant libraries of both PKR and K3L and will assess combinatorial protein functions using a yeast growth readout.

This approach will highlight residues under evolutionary constraint and will provide a glimpse into the evolutionary landscape in which PKR and K3L are bound.

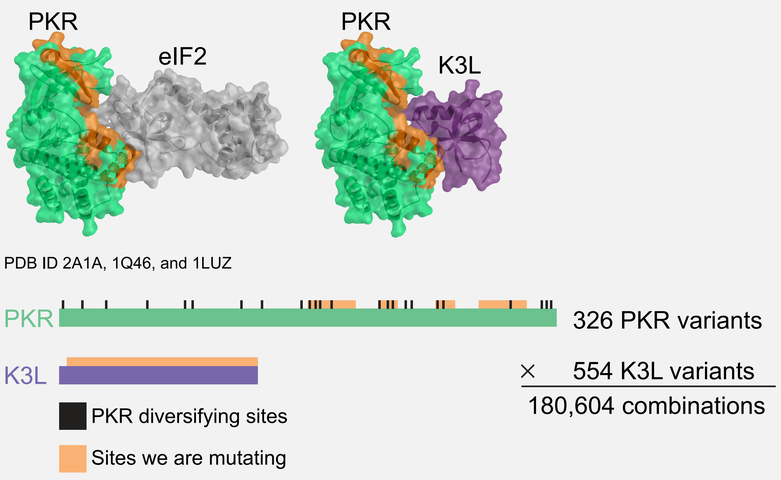
PKR and K3L interaction pathway



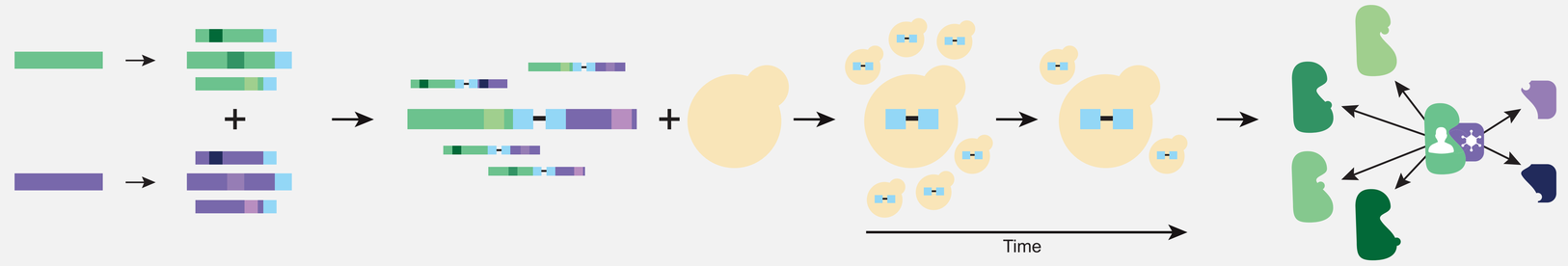
Using yeast to assess functional PKR and K3L



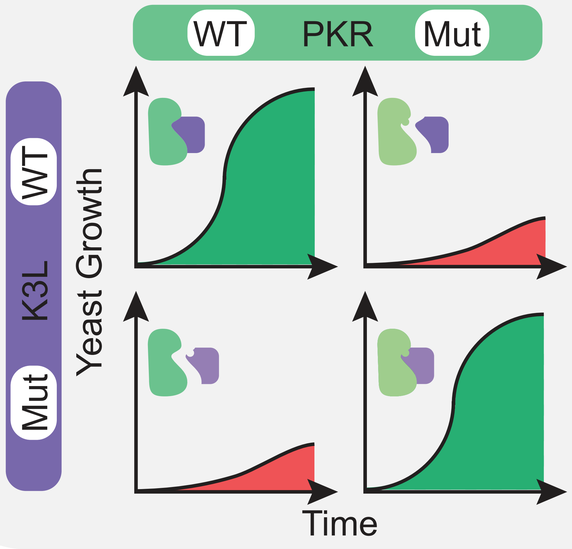
Design of PKR and K3L variants



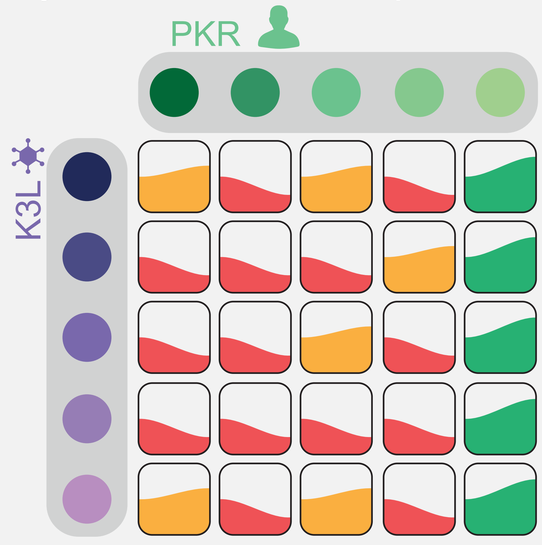
Construction and assessment of PKR-K3L variant library



Interpretation of yeast growth curves



Identify variants that alter protein function



Future Directions

Next Steps:

- Generate PKR and K3L variant libraries
- Sequence variant libraries to link variants with barcodes
- Identify evolutionary paths available to PKR and K3L

Project Extensions:

- Assess PKR variants against other viral antagonists
- Allow K3L to mutagenize at multiple sites to regain affinity to select PKR variants