Chartering the local fitness landscape of the green fluorescent protein

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The nature of the genotype to phenotype connection, the fitness landscape, and the extent to which it is shaped by the non-independent contribution of mutations, epistasis, remain poorly understood. My talk will focus on an assay of the native function, fluorescence, of tens of thousands genotypes of the green fluorescent protein, including genotypes containing multiple missense mutations, allowing for the exploration of the local fitness landscape of an entire protein coding gene with an unprecedented detail. We find that the impact of multiple missense mutations on fluorescence was influenced by epistasis, especially those in functionally important sites with a weak individual effect on fluorescence. Furthermore, although the fitness landscape can be approximated with a relatively simple unidimensional function it is also affected by multidimensional epistasis, such that a multidimensional representation of the genotype space leads to a more accurate prediction of the level of fluorescence for each genotype. The broad congruence of the estimates of the prevalence of epistasis from long-term evolution with our data suggests that our query of the shape of the local fitness landscape can be extrapolated to a larger scale. However, the local fitness landscape does not appear to be influenced by epistasis between amino acid residues with a direct interaction in the protein structure. This observation appears to contrast with the general conclusions of the importance of structural interactions in long term evolution, suggesting that multidimensional epistatic interactions are rare in short term evolution but accumulate with protein divergence.