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The Heterogeneity of Mutational Tolerance in a Protein is Dependent on the Strength of Selective Pressure Correlating with Sectors of Co-evolving Residues MICHAEL STIFFLER, RAMA RANGANATHAN, UT Southwestern Medical Center — Proteins are capable of tolerating mutations at many positions while still maintaining fold and function. Previous studies have failed to consider how tolerance to random mutagenesis might depend on the strength of selective pressure. To examine this, we measured the fitness of every single point mutation of TEM-1 beta-lactamase across a range of ampicillin concentrations utilizing a novel application of deep-sequencing. We found that the relative mutational robustness between positions varied considerably with respect to ampicillin concentration: at a low ampicillin concentration only a few positions are intolerant of mutations, while at a higher ampicillin concentration many additional positions are as equally intolerant of mutations. Using an analytic method termed statistical coupling analysis (SCA) to measure the co-variation between all positions in a sequence alignment of beta-lactamases revealed sectors of co-evolving positions associated with groups of residues having increased sensitivity to mutagenesis at either low or high ampicillin concentrations. Our findings suggest that nature has "designed" proteins to be robust to random mutagenesis by loading the constraints for fitness on discrete networks of co-evolving positions depending on the strength of selective pressure.

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