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Commentary

Mechanisms and Advantages of Enzyme Co-Localization

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DESCRIPTION

Enzyme-catalyzed processes are one of the most important and common interactions in the nature. Enzymes are essential in contemporary technology because they catalyze nearly all life-sustaining processes. Nature has optimized enzymes and enzymatic reactions in the framework of metabolic pathways to perform effectively and efficiently throughout billions of years of biological history. Understanding how natural enzymatic reactions are organized and sustained in live organisms is crucial for understanding life as well as designing and optimizing synthetic enzymatic reactions for cutting-edge biotechnological applications.

Experiment evidence has demonstrated over the last century proving that enzymes are not randomly distributed in living cells, but rather locate themselves at specific regions, on or within membranes, or form functionally important complexes. During 1857, Bernard studied sugar production in live and isolated a "glucose-forming material" that was later named glycogen. A century later, metabolic experiments suggested that glycogens are directly associated with enzymes involved in their metabolism, forming dynamic organelles or enzyme clusters called glycosomes by Scott and Still. Ever since, several other enzyme assemblies have been discovered and studied, sparking theoretical and experimental research into the understanding and optimization of enzyme clusters.

Kinetic experiments in the early 1950s suggested that intermediary metabolites could be transmitted directly between two sequential enzymes in a cascade. This observation led to the concept of substrate channeling, which occurs either as a result of enzyme proximity or within static or dynamic enzymatic complexes known as multi-functional enzymes and metabolons, respectively. These discoveries triggered intense disputes in the literature about the advantages and relevance of substrate channeling and enzyme proximity *in vivo*, which is still being discussed today. Much effort has been expended in biotechnology to create new strategies for gathering and maintaining enzymes together in the expectation of speeding up processes by shortening the diffusion route of intermediates.

In the early 1970s, it was clear that localizing or immobilizing single (non-conjugated) enzymes could change their properties, could implying useful tools for controlling and enhancing enzymatic reactions.

Methods for localizing, immobilizing, and conjugating enzymes have been developed, with the ultimate objective of optimizing single and multiple reactions. The effects and benefits of spatial proximity of two sequential enzymes are then investigated, with particular emphasis on reaction velocity, a topic of recent controversy.

The enzyme clustering or compartmentalization, with a focus on natural enzyme clusters found in living cells and an examination of models developed to optimize clusters of synthetic enzymatic reactions.

Co-localizing enzymes have a huge impact on their characteristics, such stability, specificity, and activity, and hence on reaction kinetics. Depending on changes in the local environment and enzyme shape, enzyme co-localization can have a positive or negative impact on enzyme activity. The closeness of enzymes has been inaccurately linked to improve kinetics in the case of sequential enzymes. The immobilization of GOx and HRP on a DNA origami to speed up the GOx-HRP reaction pathway is a notable case. Instead, they used a tiny molecular linker to connect the two enzymes and found no improvement, even in the presence of catalase, an enzyme that competes with HRP for hydrogen peroxide.

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