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## Coupling Between Metabolism and Compartmentalization: Vesicle Growth in the Presence of Dipeptides

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**Introduction:** A fundamental unresolved question in studies on the origin of life is: how different, ubiquitous protocellular functions begun to work in concert setting the stage for Darwinian evolution of nascent life? From this perspective, of particular significance is coupling between growth of protocellular compartments and the encapsulated, primordial metabolism, which is one of the focal topics of the current ISSOL meeting. Specifically, growth and division of cells facilitated by the products of a metabolic reaction would confer an evolutionary advantage on protocells encapsulating this reaction, as their population would increase at the expense of other protocells. Along these lines, Adamala and Szostak [1] have recently demonstrated that a dipeptide captured inside fatty acid vesicles catalyzes the formation of other dipeptides from activated monomers. Some of the newly synthesized dipeptides, in turn, are capable to promote competitive growth of vesicles in the presence of fatty acid micelles. As vesicles become larger, they adapt filamentous shape, which has been shown to promote their division [2]. On the basis of computer simulations, we provide a molecularly detailed explanation of this process and draw conclusions about its generality.

**Results and Discussion:** Extensive molecular dynamics simulations were carried out to understand interactions of dipeptides with vesicles and their functional role in fusion of fatty acid vesicles with micelles. Dipeptides containing hydrophobic amino acids, such as leucine and phenylalanine, were shown to accumulate at the water-membrane interface, in contrast to dipeptides containing only hydrophilic residues, such as Ser-Ser. Hydrophobic dipeptides, Val-Val, Leu-Leu, Phe-Phe, and Phe-Leu, were found to form hydrophobic clusters at the surface of vesicles that promoted mixing of hydrophobic fatty acid tails from vesicles and micelles in contact along a low energy pathway. The enhancement of fusion correlated with the hydrophobicity of the dipeptide; the shortest fusion time of 1-2  $\mu$ s was found for Phe-Phe whereas the longest time of 20  $\mu$ s was observed for the least hydrophobic, Val-Val peptide. In contrast, no fusion was observed during simulations in the absence of dipeptides. Hydrophobic dipeptides at membrane surfaces were also found to lower the energy barrier and enhance the rate of fatty acid flip-flop in the membrane by 50%. This promotes a faster proton transfer across protocellular walls, which could be important for early energy transduction and metabolism [3]. Since the mechanism of vesicle growth and proton transfer described here is general, other metabolites and small peptides that tend to accumulate at the water-membrane interface [4] might have carried out the same function. This illuminates a universal way of coupling metabolism and compartmentalization.

**References:** [1] Adamala K and Szostak JW (2013) *Nature Chemistry* 5:495–501. [2] Zhu TF et al. (2012) *Proceedings of the National Academy of Sciences U.S.A.* 109:9828–9832. [3] Chen IA and Szostak JW (2004) *Proceedings of the National Academy of Sciences U.S.A.* 101:7965–7970. [4] Pratt LR and Pohorille A (2002) *Chemical Reviews* 102:2671-2692.