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Communicating artificial cells

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Intercellular chemical communication is commonly exploited for the engineering of living cells but has been largely ignored by efforts to build artificial cells. Since communication is a fundamental feature of life, the construction of artificial cells capable of chemical communication will likely lead to a deeper understanding of biology and allow for the development of life-like technologies. Herein we highlight recent progress towards the construction of artificial systems that are capable of chemically communicating with natural living cells. Artificial systems that exploit both biological and abiological material for function are discussed.

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Introduction

Communication is a fundamental feature of life. All living organisms actively communicate with their surroundings to better their chance of survival through the coordination of group behavior. Although several different mechanisms exist to exchange information, chemical communication is one of the most universal. The secretion and detection of chemicals, for example autoinducers and pheromones, is used to facilitate mating, the search for food, cellular recognition, and the evasion of host defense mechanisms. Such involuntary forms of communication may depend on the exchange of small molecules [1] or proteins [2]. For example, bacteria communicate with N-acyl homoserine lactones and peptides, and many animals signal territory through scent marking, often by exploiting major urinary proteins [3].

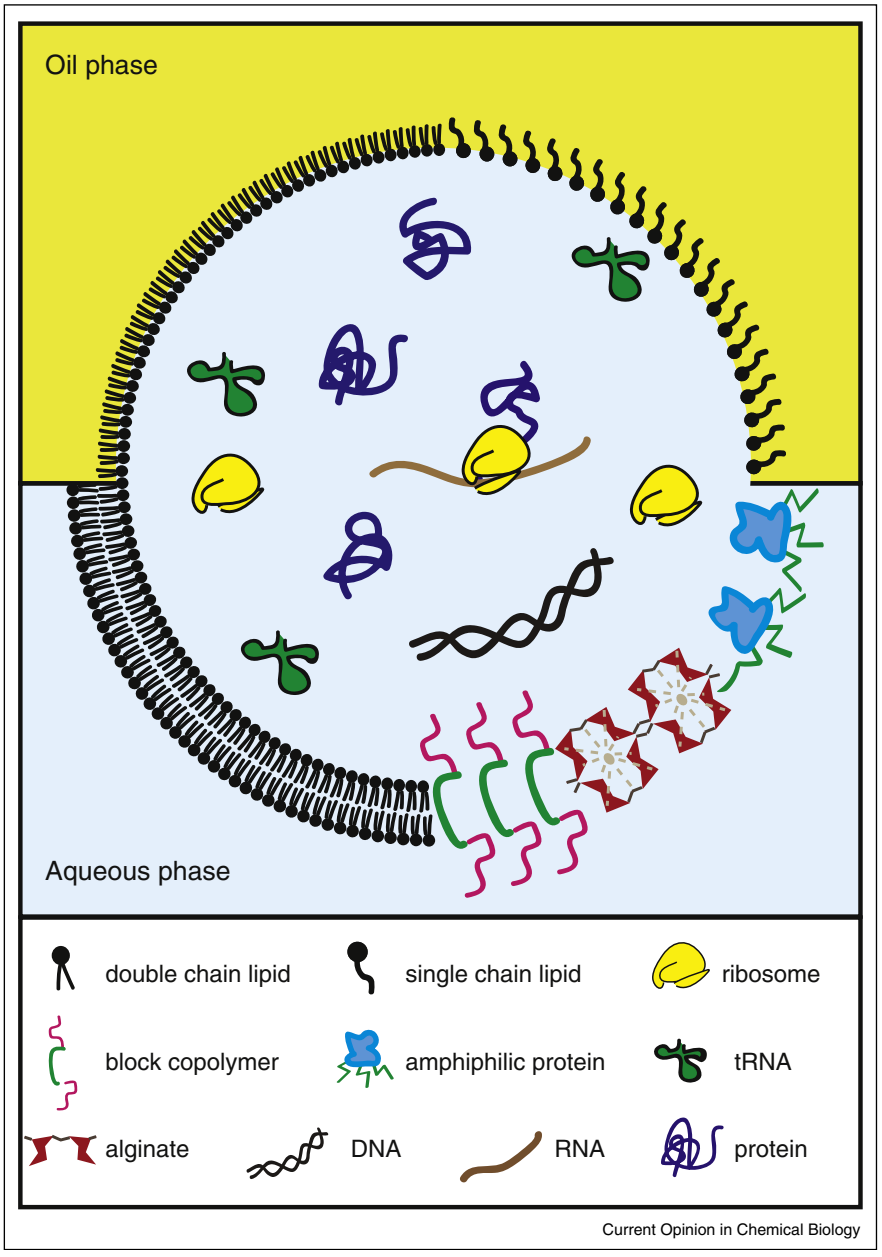
The prevalence of chemical communication may be rooted in the types of pathways needed for early life to have survived. A rudimentary sense-response mechanism to avoid environments devoid of nutrients would seem to have been necessary since organisms themselves consume local resources and secrete waste material [4]. Contemporary cells sense and respond to their internal and external environment, continuously adapting to fluctuating conditions. This is just as true for mammalian cells as it is for bacteria. Stem cell differentiation is controlled by environmental conditions [5], and bacterial gene expression is regulated by many external factors, including pH, temperature, and the presence of other bacteria through the detection of metabolic end products [6].

Chemical communication pathways are now commonly exploited for the engineering of both prokaryotic and eukaryotic cells. The construction of pathways that exploit cellular communication provides new avenues from which to gain a deeper understanding of biology and creates opportunities for the generation of new forms of living technologies. However, as with all technologies, there are limitations. Living cells are not static, but rather grow and evolve, meaning that an engineered pathway may no longer function as intended in the future. Replicating systems may be easier to produce once one copy is made, but it is more difficult to maintain and contain living cells. One alternative approach is to construct non-living, cellular mimics (i.e. artificial cells) that provide the desired functionality. Artificial cells typically consist of a lipid vesicle that contains DNA and transcription-translation machinery, although deviations from this composition are possible (Figure 1). Since artificial cells are built form the ground up, only the biological features that are needed for the intended function are incorporated while the remaining cellular baggage is left out. For example, an artificial cell can be made to produce a drug molecule in response to a pathogen but lack the ability to replicate. Such a system could serve their intended function for a short period of time and then decompose, returning the surroundings to their original state.

Engineered communication between living cells

The engineering of living cells has progressed much more rapidly than that of artificial cells. Therefore, a look into what has been accomplished with living systems can reveal the possibilities and available tools for the engineering of artificial cells. Most frequently, the exploited communication paths depend on the harnessing of natural intercellular signaling pathways. Bacteria assess their population density in part through the secretion and detection of small molecules (autoinducers) that regulate several physiological processes, including biofilm formation, bioluminescence, and virulence [7]. One of the most studied quorum signaling pathways is that of *Vibrio fischeri*, which depends on the production of small molecules known as

Figure 1



The composition of an artificial cell. The membrane can consist of a variety of molecules, some of which stabilize bilayer vesicle structures while others stabilize a water-in-oil emulsion droplet. The compartment has all of the components needed for the cell-free expression of mRNA and protein. Note that alginate would not be solely located at the boundary of the artificial cell.

acyl homoserine lactones. Gram-negative bacteria typically use acyl homoserine lactones for intraspecies communication, whereas Gram-positive bacteria often use small, auto-inducing peptides. Communication can also be between different bacterial species, as exemplified by the pathways that exploit autoinducer 2 (AI-2), a molecule synthesized and sensed by several different Gram-negative and Gram-positive bacteria [8].

Engineered communication paths often times involve the transplanting of quorum signaling components from one organism to another. However, rather than monitoring the cell density in order to, for example, initiate biofilm formation, quorum sensing is combined with different output functions, such as the synthesis of a toxin in order to maintain a desired concentration of cells [9]. Alternatively, bacteria can be engineered to overexpress components of