Intracellular/surface proteins in pathogens: Another purpose in another place?

Bacteria use proteins on their surface to interact with host cells and tissues during infection. Proteins on the bacterial cell surface can also be good targets for developing new vaccines. The significance of surface proteins prompted many research groups to find out what types of proteins are found on the surfaces of dozens of bacterial species. Our paper summarizes our analysis of the results of twenty-two such studies.

Surprisingly, hundreds of proteins that are found on the cell surface were already known to have key functions inside the cell. When intracellular proteins are reused for a different function on the cell surface, they are called “intracellular/surface moonlighting proteins” (Fig 1). Many of the proteins found on the cell surface are involved in central metabolic pathways, including some that have previously been shown to have a moonlighting function on the cell surface in at least one species, such as Hsp60/GroEL, DnaK, glyceraldehyde 3-phosphate dehydrogenase, enolase, and fructose 1,6-bisphosphate aldolase. Hundreds of other intracellular proteins are also found on the cell surface, although a second function on the surface has not yet been demonstrated, for example, glutamine synthetase, gamma-glutamyl phosphate reductase, and cysteine desulfurase. Our study shows that the presence of intracellular proteins on the cell surface is more common than previously expected and suggests that many additional proteins might be candidates for being intracellular/surface moonlighting proteins, or in other words, are likely to have an important function on the cell surface and not simply observed there due to experimental artifacts.

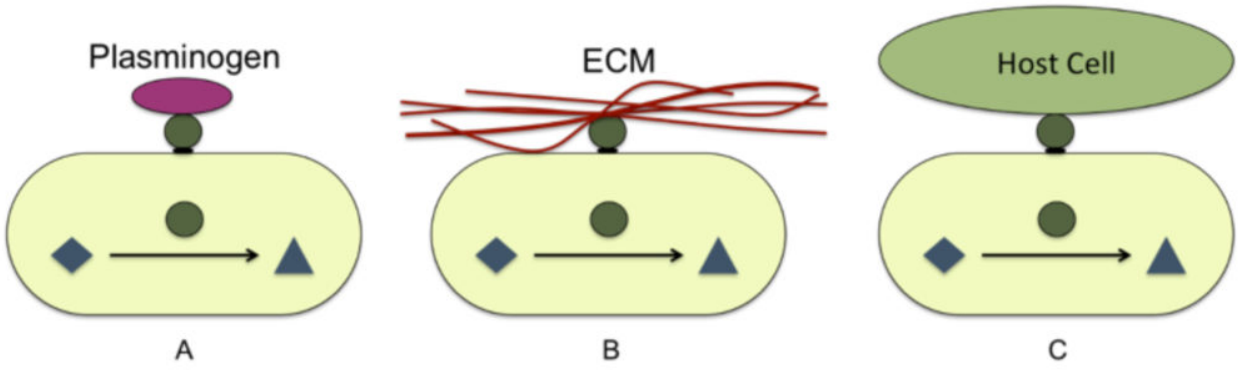

Fig. 1. Intracellular proteins that perform another function on the cell surface. An intracelllar/surface moonlighting protein can function as an enzyme inside of the cell, converting a substrate (diamond) to a product (triangle) (A-C) and can also be present on the cell surface. Some of them can bind to plasminogen and convert plasminogen to plasmin (A), or bind to extracellular matrix (ECM) proteins such as fibronectin, collagen and laminin, or interact with host cell surface proteins (C). These intracellular proteins on the cell surface often play an important role in invasion, infection and virulence.

Importantly, our bioinformatics analysis of these intracellular/surface moonlighting proteins found that the majority do not have the characteristics needed to be secreted from the inside of the cell to the outside of the cell through any known mechanisms of secretion. They also do not possess any of the known physical characteristics needed to attach them to the cell surface. The large number of intracellular proteins found on the cell surface without any known mechanism of secretion or attachment to the cell surface strongly suggests there must be additional, as yet unknown, mechanisms for these proteins to be secreted from the cell and also to become attached to the surface of the cell. Understanding how these proteins are secreted and attached to the cell surface could lead to novel therapeutics for treating infections that interfere with these pathways.

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Publication

An analysis of surface proteomics results reveals novel candidates for intracellular/surface moonlighting proteins in bacteria.
Wang W, Jeffery CJ
Mol Biosyst. 2016 Apr 26