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Author for correspondence:
Constance J. Jeffery
e-mail: cjeffery@uic.edu

Protein moonlighting: what is it, and why is it important?

Constance J. Jeffery

Department of Biological Sciences, University of Illinois at Chicago, Chicago, IL 60607, USA

CJJ, 0000-0002-2147-3638

Members of the GroEL/HSP60 protein family have been studied for many years because of their critical roles as ATP-dependent molecular chaperones, so it might come as a surprise that some have important functions in ATP-poor conditions, for example, when secreted outside the cell. At least some members of each of the HSP10, HSP70, HSP90, HSP100 and HSP110 heat shock protein families are also 'moonlighting proteins'. Moonlighting proteins exhibit more than one physiologically relevant biochemical or biophysical function within one polypeptide chain. In this class of multifunctional proteins, the multiple functions are not due to gene fusions or multiple proteolytic fragments. Several hundred moonlighting proteins have been identified, and they include a diverse set of proteins with a large variety of functions. Some participate in multiple biochemical processes by using an active site pocket for catalysis and a different part of the protein's surface to interact with other proteins. Moonlighting proteins play a central role in many diseases, and the development of novel treatments would be aided by more information addressing current questions, for example, how some are targeted to multiple cellular locations and how a single function can be targeted by therapeutics without targeting a function not involved in disease.

This article is part of the theme issue 'Heat shock proteins as modulators and therapeutic targets of chronic disease: an integrated perspective'.

1. Introduction

HSP60/GroEL heat shock proteins (HSPs) have been studied for many years because of their critical role as ATP-dependent molecular chaperones, but some have important functions in ATP-poor conditions, when secreted outside the cell. In fact, members of each of the HSP60/HSP10, HSP70, HSP90, HSP100 and HSP110 HSP/chaperone protein families have been found to be 'moonlighting proteins'. Moonlighting proteins comprise a subset of multifunctional proteins in which one polypeptide chain exhibits more than one physiologically relevant biochemical or biophysical function [1]. In this class of multifunctional proteins, the multiple functions are not due to gene fusions or multiple proteolytic fragments. Several hundred moonlighting proteins have been identified, and they include a diverse set of proteins with a large variety of functions [2].

Among the first proteins to be recognized as performing two very different functions in the same organism were the taxon-specific crystallins. Crystallins make up a large part of the lens of the eye, and about a dozen are identical to catalytically active ubiquitious enzymes. For example, the epsilon crystalline found in birds (mallard duck, swans, geese and ostriches) and reptiles (crocodiles) [3–5] is the same protein as lactate dehydrogenase, which catalyses the interconversion of pyruvate and lactate and is found in many cell types in almost all species (figure 1). In other species, different enzymes were co-opted to serve as crystallins—quinone oxidoreductase is the zeta crystalline in camels, llamas, guinea pigs and frogs [6–8], and aldehyde dehydrogenase is the eta crystalline in elephant shrews [9].

Other soluble enzymes have evolved to serve a second function as transcriptional or translational regulators that bind DNA or RNA, respectively, in some

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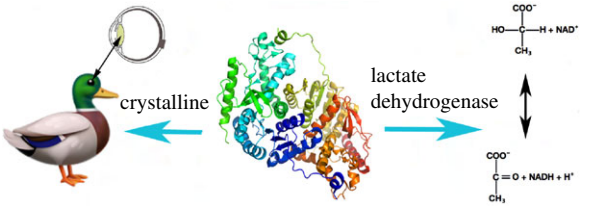

Figure 1. A moonlighting protein can have two very different functions in the same species. For example, in ducks, the epsilon crystalline found in the lens of the eye is the same protein as the ubiquitous enzyme lactate dehydrogenase, which catalyses the interconversion of pyruvate and lactate. (Online version in colour.)

cases as a feedback mechanism to regulate the level of expression of enzymes in the same biochemical pathway. Aconitase catalyses the isomerization of citrate to isocitrate in the citric acid cycle. When cellular iron concentrations decrease, the iron–sulfur cluster in the active site pocket is lost and the protein changes conformation. The new protein conformation binds RNA to regulate the expression of genes encoding proteins involved in iron uptake [10–12].

Moonlighting proteins are found throughout the evolutionary tree—bacteria, archaea, mammals, reptiles, birds, fish, worms, insects, plants, fungi, protozoans and even viruses. They include enzymes that serve as receptors, secreted cytokines, transcription factors, DNA stabilizers, components of the cytoskeleton or proteasome subunits. Other combinations of functions include a receptor and transcription factor, chaperone and cytokine, DNA-binding protein and component of the extracellular matrix, transmembrane channel and regulator of other channels, and components of the ribosome that are transcription factors.

2. Intracellular/extracellular moonlighting proteins

One of the largest subgroups of moonlighting proteins identified to date are intracellular chaperones and enzymes that play a different role outside the cell (figure 2). These are often 'housekeeping proteins' that are widespread in evolution and function in glycolysis, the citric acid cycle, the pentose phosphate pathway, and protein and DNA metabolism. The first to be identified was a glyceraldehyde 3-phosphate dehydrogenase (GAPDH) on the surface of pathogenic streptococci [13]. Many other intracellular/cell surface enzymes were later found, including other GAPDHs [14–28], phosphoglycerate kinase [29,30] and enolase [31–54]. Other intracellular/cell surface proteins (ICSPs) include chaperones (HSP60/GroEL, HSP70/DnaK) [54–58], a protein synthesis elongation factor (Ef-Tu) [59–61] and a histone (H1) [62].

Some of these proteins function as cell surface receptors in humans and other mammals. GAPDH catalyses the conversion of D-glyceraldehyde 3-phosphate to 3-phospho-D-glyceroyl phosphate in glycolysis inside the cell in most cell types but in mammals also serves as a cell surface transferrin receptor to aid in iron uptake [63,64]. The HSP60 HSP is a chaperone assisting mitochondrial protein import in the cell, and is a cell surface receptor for high-density lipoproteins through its affinity for apolipoprotein apoA-II [65].

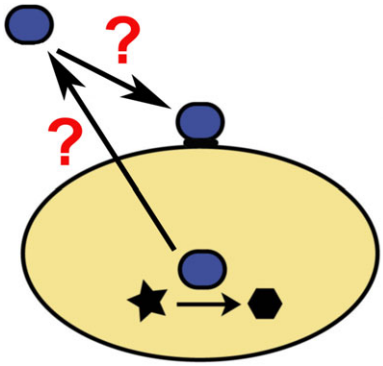

Figure 2. Several dozen moonlighting proteins have different functions inside and outside the cell. Many housekeeping proteins, including enzymes that convert a substrate (star) to a product (hexagon) or chaperones that assist in protein folding, have a second function when secreted or when attached to the cell surface. In most cases, how the intracellular/surface or intracellular/secreted moonlighting proteins are secreted and how some become attached to the cell surface are unknown. (Online version in colour.)

In humans, pyruvate kinase 3 (PK3) isoform 2, glutathione S-transferase Mu 3, triosephosphate isomerase and fructose-bisphosphate aldolase A play a second role on the sperm head membrane, where they are involved in interactions with zona pellucida proteins of egg [66–68].

This phenomenon of intracellular/surface moonlighting proteins has been observed widely in bacteria. Bacteria (and other pathogens) commonly use moonlighting cytosolic proteins on the cell surface for forming and maintaining interactions with the host species. Some of these proteins play important roles in infection, invasion, virulence and formation of biofilms. Colonization requires adhesion to the host, and many surface proteins bind to proteins in the extracellular matrix, including fibronectin, laminin, and/or collagen, or to mucin, a component of the mucosal epithelial lining. Other surface moonlighting proteins bind directly to proteins on host cell surfaces. These interactions enable a physical attachment to the host. *Listeria* makes use of alcohol acetaldehyde dehydrogenase/Listeria adhesion protein (LAP) to bind to intestinal epithelial cells [55]. Enolase in glycolysis has been found on the cell surface in many species of bacteria (*Streptococcus*, *Mycoplasma* and *Plasmodium falciparum*) where it plays a role in binding plasminogen, fibronectin, and other proteins and is important in infection of human, canine and avian hosts [69–72]. Translation Ef-Tu from *Streptococcus gordonii* binds to host mucin [73]. *Streptococcus pneumoniae* makes use of endopeptidase O to bind host plasminogen and fibronectin [74]. The GAPDH of *Haemonchus contortus* (barber pole worm), a nematode species that infects sheep and goat gastrointestinal tracts, binds the alternative complement pathway protein C3, inhibits the complement cascade, and helps the pathogen evade host immunity [75]. The HSP70/DnaK chaperone also serves as a cell surface receptor for plasminogen in many species—*Neisseria* [76], *Mycobacterium tuberculosis* [77], *Bifidiobacterium lactis* [78], etc.

Streptococcus pneumoniae and the many other pathogenic bacteria that use enolase GAPDH or other enzymes to bind plasminogen help the zymogen get converted to the active protease plasmin by using an endogenous protease or making use of the host's tissue-type plasminogen (tPA) activators and urokinase-type plasminogen activators [79,80].

The now active plasmin attached to the surface of the invading organism can be used as a general protease to digest host extracellular matrix and basement membrane, thereby assisting migration through tissues.

These interactions between cytoplasmic/cell surface moonlighting proteins with host tissue are not always the result of disease or infection. The commensual 'probiotic' bacterium *Lactobacillus acidophilus* uses GAPDH on its surface to help colonize the gut. In this case, the bacterial GAPDH binds to host mucin [81].

Moonlighting cytosolic proteins are also often used as secreted signalling molecules to regulate other cell types within an organism, or to modulate host responses in the case of a pathogen. Inside the cell, members of the HSP60/HSP10, HSP70, HSP90, HSP100 and HSP110 protein families are protein chaperones that prevent client proteins from misfolding and promote correct refolding and assembly of protein complexes, and members of each protein family have been identified that have additional functions outside the cell. The extracellular roles of mammalian members of these protein families are discussed further in other papers in this collection, so in this review the focus is on other examples of cytoplasmic proteins that perform other functions when secreted. Thymidine phosphorylase, an enzyme in pyrimidine metabolism, is the same protein as the secreted platelet-derived endothelial cell growth factor (PDGF) [82]. Lysyl-tRNA synthetase, which attaches lysine to tRNA for use in protein synthesis, acts extracellularly on macrophages and peripheral blood mononuclear cells to increase TNF-α production and target cell migration [83]. Thymosin β-4 is an intrinsically disordered protein involved in sequestering G-actin (monomeric actin) to prevent its polymerization to F-actin in polymorphonuclear leucocytes. Thymosin β-4 sulfoxide is generated in monocytes by the oxidation of a methionine (Met6) in the presence of glucocorticoids and is secreted to inhibit the anti-inflammatory response [84–87]. Phosphoglucose isomerase (PGI, also known as glucose-6-phosphate isomerase, autocrine motility factor, neuroleukin, differentiation and maturation mediator) catalyses the interconversion of glucose-6-phosphate and fructose-6-phosphate in glycolysis and gluconeogenesis, and is an extracellular cytokine/growth factor that binds to target cells and causes pre-B cells to mature into antibody secreting cells, supports the survival of embryonal neurons, and causes differentiation of several leukemia cell lines [88–94]. In the black footed ferret (*Mustela nigripes*), PGI was also found to be necessary for embryo implantation [95]. The growth factor effect of PGI can also play a role in disease. Extracellular PGI causes an increase in cell migration during breast cancer metastasis. Another cytoplasmic protein that also has roles in cancer development, threonyl aminoacyl-tRNA synthetase (TARS), is secreted from endothelial cells in response to TNF-α and VEGF and promotes vascular development. An association has been observed between TARS expression and advancing stage of ovarian cancer [96]. A mutation that prevents TARS synthetase activity is still active in promoting vascular development.

Some bacterial cytosolic enzymes are secreted to interfere with host defenses. GAPDH from *A. vaginae* is secreted to interfere with human C5a anaphylatoxin [97]. *Leishmania donovani* secretes another glycolytic enzyme, fructose-bisphosphate aldolase, as well as translation elongation factor EF-1 to cause activation of host macrophage protein tyrosine phosphatase-1 (SHP-1) and decreased activity of infected macrophages [98,99]. The GroEL/60 kDa chaperonin produced by *Enterobacter aerogenes*, the bacterial endosymbiont of an insect, antlions, is secreted and used as toxin to paralyze cockroaches [100]. Enolase from the nematode *Steinernema glaseri*, when on its cuticle surface or secreted in to the host hemolymph, suppresses its insect host's immune system [101].

Further examples of intracellular/surface/secreted moonlighting proteins are included in our list of moonlighting proteins in the MoonProt Database [2]. Most of the known ICSPs are from bacteria, although examples are found throughout the evolutionary tree. The bacterial species represented include typical Gram-positive and Gram-negative species, as well as mycobacteria, spirochetes and mycoplasma. In addition, many more cytoplasmic proteins have been found to be secreted or bound to the cell surface through proteomics studies. For most of the proteins found through proteomics studies, further experiments are needed to determine if the protein has a second function outside the cell, if it performs the same function as when inside the cell, or perhaps was found in the extracellular location due to experimental artefacts of the proteomics methods that were used.

3. Structural basis for intracellular/extracellular functions

One question that arises when a protein is found to be a moonlighting protein pertains to how one polypeptide chain can perform two different functions, because protein function is tied to protein structure and it might be presumed that it would be necessary to alter a protein structure a lot to gain a new function, which could result in loss of the original function. Some moonlighting proteins have been found to solve this problem of switching between functions by undergoing large conformational changes or transitions between intrinsically unfolded domains and multiple distinct folded structures so that different conformations of the protein structure can perform different functions. By contrast, for many of the intracellular/extracellular moonlighting proteins, large diversions from the structure or conformation performing a catalytic or chaperone function within the cell are not needed for performing the extracellular function. In many of the cases discussed above, the extracellular function involves binding to another molecule, often another protein. In addition to an active site pocket where catalysis occurs when the protein is inside the cell, the three-dimensional structure of an enzyme or chaperone includes a large amount of solvent exposed surface area. Through millions of years of evolution some portion of this surface can gain a pattern of amino acids needed for interacting with another molecule, whether a small molecule, a cell surface receptor, or another protein, without affecting the active site pocket [102]. This new binding site does not need to very large or complex. Ehinger and co-workers found that in the case of *Streptococcus* enolase, a small motif consisting of only nine amino acids (248FYDKERKVY256) containing lysines and negatively charged residues was sufficient for binding to plasminogen. The evolution of this binding site did not affect the ability of enolase to catalyse the reaction, and the overall subunit fold of the protein is identical to that of enolase proteins that are not known to bind plasminogen [103].

4. Regulation of multiple activities

Having the ability to perform multiple functions is often only part of the story for moonlighting proteins. The correct level of each of the multiple protein activities in the correct place and the correct time can also be important for maintaining health and homeostasis. Changes in the expression, level of activity and/or location of moonlighting proteins play a central role in many diseases. Mutations that result in altered activity of a moonlighting protein can lead to disease—whether it is a decrease in activity, or, in some cases, an increase in activity, for example, by disrupting the careful checks and balances of the immune system. In addition, mutations that change the amino acid sequence of a protein can on rare occasions result in an increase in function or a different function, sometimes referred to as 'neomorphic moonlighting function' if it adds a new catalytic function or results in aggregate formation [104]. The location and timing of each protein activity is also important. Sufficient amounts of protein need to be expressed by the appropriate cell types. The expression needs to occur at the correct time in development, and/or appropriately in response to signals in the environment. It is a common observation in libraries of gene knockouts that some gene knockouts result in death of the embryo even though the gene is expected to function only in the adult organism. It is likely that some of these genes encode moonlighting proteins that have additional functions during embryogenesis.

Once the correct level of protein is attained, each of the functions of a moonlighting protein needs to be performed at the appropriate level. A moonlighting protein might perform multiple functions simultaneously, each might be independently regulated, or it might alternately perform one or the other function and have a means of switching between them. A change in protein conformation as in aconitase, mentioned above, is one method of switching between functions. Post-translational modifications (PTMs) are commonly used to regulate protein function in general, and they can be used to prompt a moonlighting protein to switch to a different function. For example, several protein components of the ribosome become phosphorylated and leave the ribosome to enter the nucleus where they participate in other activities. Ribosomal protein S3 (rpS3) has additional functions in the nucleus in DNA damage repair and as a transcription factor [105,106]. L10a (rpL10a) can interfere with gemnivirus reproduction in plants [107,108]. L13a (rpL13a) joins a multiprotein transcription factor [109]. By contrast, the oestrogen receptor leaves the nucleus when it undergoes palmytoylation so that it can interact with a signalling pathway at the plasma membrane [110]. Whether because of PTMs or other means of targeting, many other moonlighting proteins also perform their different functions in different cellular locations, whether in the cytoplasm, in the nucleus, in or attached to another organelle, at the cell membrane, or outside the cell.

5. Secretion of intracellular/surface moonlighting proteins

While signals for switching between functions are known for some moonlighting proteins, less is known about how a portion of the cytosolic pool of an intracellular/surface moonlighting protein becomes targeted for secretion. There are several lines of evidence that the ICSPs are indeed secreted and do not get out of the cell due to cell leakage or cell death (reviewed in [111]). When secretion of intracellular/surface moonlighting proteins is observed, many other cytoplasmic proteins are not found in the supernatant, and the proteins found in the supernatant or on the cell surface do not correlate with the most abundant proteins in the cell. In *Staphylococcus aureus*, the highest level of secretion of enolase and aldolase is during exponential growth, when cell breakage is at a minimum [112]. In addition, for *Escherichia coli* enolase, single amino acid substitutions at K341 resulted in a loss of its secretion, even of a mutant protein that is still catalytically active [113]. Similarly, in *Bacillus subtilis* enolase, deletion of an internal α-helix also prevented secretion [114]. These results support the idea that there is likely to be a secretion system(s) for at least some intracellular/surface moonlighting proteins.

The system or mechanism by which the majority of cytoplasmic proteins with a second function outside the cell are secreted is not known (figure 2). The intracellular/surface moonlighting proteins do not contain an N-terminal signal sequence required for secretion by the canonical Sec secretion system. They also do not contain other sequence motifs, such as a twin arginine leader motif required for secretion by the bacterial TAT system. There are several additional non-canonical secretion systems, but the other secretion systems are generally used for transport of only a few specific proteins, for example, the type 1 secretion system (T1SS) in Gram-negative bacteria. In particular, a secretion system in which a large portion of the pool of each protein type remains inside the cell but some of the pool of the protein partitioned to the cell surface has not been identified. This may involve a novel version of a known secretion system or it may involve an as-yet-unknown secretion system. In mammals, some of the secreted moonlighting proteins are found in secretory lysozomes or exosomes, but how they are targeted there is not clear. How these intracellular/surface/secreted moonlighting proteins are selected for secretion, and why only a portion of the cytoplasmic pool of the protein is secreted are current questions in the field.

The mechanism(s) by which some moonlighting proteins become attached to the cell surface is also unknown. The mechanism of cell surface attachment could potentially be a part of a secretion mechanism, although some recombinantly expressed and purified intracellular/surface moonlighting proteins are capable of reattaching to the cell surface. With a few exceptions [115] most of the ICSPs do not contain known amino acid sequence or structural motifs for attaching to the cell surface. Cell surface attachment could involve a new version of a known mechanism or it may involve an as-yet-unknown mechanism.

6. New targets for therapeutics

The development of novel treatments of diseases involving HSPs or other moonlighting proteins would be aided by more information about their targeting and their functions. For many of the human intracellular/extracellular moonlighting proteins, there is still much to learn about their roles in disease, but many have been implicated in autoimmune disease, heart disease, obesity, diabetes and cancer. The current knowledge of the roles of HSPs in immunology and cancer is discussed in other articles in this collection. In general, for a

moonlighting protein, it is important to identify and understand both functions as well as their regulation and targeting. It is necessary to clarify which of the functions of a moonlighting protein is involved in disease development so that the correct protein function can be targeted for the development of novel therapeutics without causing side effects due to targeting a function not involved in disease. This also extends to the roles of paralogs, and also splice variants in humans, because they can share all, some, one, or none of the functions of a moonlighting protein. Clarification of when and where each function is performed by each version of the protein is also important if the protein is to be used as a biomarker.

Elucidating how intracellular/cell surface/secreted moonlighting proteins are secreted might identify processes and proteins that are involved in the novel secretion systems (or additional versions of known secretion systems) or surface attachment mechanisms that could serve as novel targets for developing new strategies for controlling infection. Understanding how intracellular/cell surface moonlighting proteins are targeted to the surface of a pathogen might lead to a method to decrease the ability of bacteria to bind to host tissues and could provide new targets for developing therapeutics to treat infections. With the increasing problem of antibiotic resistance, new targets for inhibiting bacterial infection and virulence are needed.

7. Conclusion

Hundreds of proteins have been found to have multiple, apparently unrelated functions. A large portion of these, including many HSPs, are cytosolic proteins that have been found to have additional functions when targeted to the cell surface or secreted, and the results of cell surface proteomics studies suggest many more might join that group. There is still much to be learned about their roles in health and disease, especially the sometimes complex signalling functions of many secreted mammalian proteins. In the case of bacterial and other pathogens, elucidating the proteins needed for their secretion and membrane attachment could lead to novel treatments for infections.

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