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Popular Article

# Moonlighting Proteins: Brid's Eye View on Basics and Importance

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***Abstract***

Moonlighting proteins are a class of proteins that have been identified in the last few decades that perform two or more distinct and physiologically meaningful biochemical or biophysical functions. These functions are not brought about by pleiotropic effects, gene fusions, or a variety of RNA splice variants. Moonlighting proteins play an important role in biology and medicine. Cytosolic enzymes, DNA compactors, cytokines, DNA binding proteins etc. are some of the most common examples of moonlighting proteins. They are found in animals, humans, plants, viruses and hence are ubiquitous in occurrence. Due to this they are involved in many important physiological functions as well as are associated with variety of diseases. This article discusses about basics and importance of moonlighting proteins in today's world.

**Key Words:** Moonlighting Proteins, Diseases, Pleiotropy

**Introduction**

Proteins are large molecules made up of thousands of amino acids, all linked in a chain, and are often referred to as macromolecules. Most proteins are known to only have a single function but during the last decade, a growing number of multifunctional proteins have been discovered. Hundreds of proteins that carry out two or more unique and physiologically significant biochemical or biophysical functions- that is, functions not caused by, numerous RNA splice variants, pleiotropic effects, or gene fusions have been discovered in the last several decades, are called moonlighting proteins. The term "moonlighting proteins" was first used by Jeffery in 1999.

These moonlighting proteins are found throughout the evolutionary tree, in the three domains of life comprising eukaryotes, bacteria, and archaea. There is a database for moonlighting proteins that provides data about different functions performed by a single protein called the MoonProt Database. This database has about 200 reported moonlighting proteins, which is growing considerably day by day. There are approximately five known moonlighting proteins in archaea, about less than a hundred in eukaryotes, and around a hundred in bacteria (Henderson and Martin, 2014). Crystallin, which is a soluble enzyme with



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a secondary purpose as a structural protein in the eye's lens, was among the earliest moonlighting proteins to be identified.

A unique class of multifunctional proteins is made up of moonlighting proteins, which carry out independent, unrelated functions. The basis for the proteins to be moonlighting proteins is that they shouldn't be a result of gene fusion, that is, proteins with numerous functions resulting from gene fusion are not considered moonlighting proteins. Proteins that are translation products of various splice variants of the same gene are also not considered as moonlighting proteins. It's easy to confuse moonlighting and pleiotropism, but moonlighting proteins carry out a variety of different mechanisms, rather pleiotropic effects arise from the inactivation of a single function that is engaged in various physiological processes.

One more important criterion for moonlighting proteins is that if a protein has two or more functions, they should be independent of each other, that is deactivating one function shouldn't influence other functions of the protein. Examples of moonlighting proteins include enzymes, receptors, ion channels, and chaperones. Enzymes apart from their catalytic activities, also perform various unrelated functions in signal transduction, transcriptional regulation, DNA maintenance, or apoptosis (Huberts and van der Klei, 2010)

Many factors influence the probability that a protein will acquire the moonlighting functions. The proteins that enhance fitness, and are involved in almost all growth conditions might have the highest chance of becoming a moonlighting protein. Seven out of ten glycolytic enzymes employed in glycolysis exhibit moonlighting functions, also in the tricarboxylic acid (TCA) cycle, seven out of eight enzymes function as moonlighting proteins (Kim and Dang, 2005).

The moonlighting proteins acquire a new function as a result of random interactions with a new another protein, DNA, or RNA. As the whole protein surface is not used in its canonical function and allows (by mutations) other binding interaction that doesn't influence its original function and is beneficial then natural selection will favour this mutation. On the other hand, moonlighting proteins can be a result of mutations that alter the position of binding partners or the timing of expression of two proteins that were already capable of binding but were never in the same alignment to bind before.

A protein that performs effectively in both its original and moonlighting roles may result from mutations in the milieu of gene amplification. Gene amplification is the most frequent type of mutation which is also called gene duplication, and it allows reading of the sequences more carefully to mitigate the ability of other alleles to buffer INDEL mutations in a single allele as there are various targets for mutation in a gene. Gene duplication is the term that is usually used in the case of a single gene in an amplified region, but in the case of proteins, segmental duplication is a more appropriate term because amplification generally involves larger segments than a single gene. The frequency, method, size, copy number, and gene content of a duplicated or amplified region affect the moonlighting protein's evolution. Therefore, moonlighting proteins may be the result of the process that starts with gene amplification. However, parameters of gene amplification or duplication may be different between different organisms and in the sites of the same genomic DNA.

One possible scenario is that a gene that codes for a bifunctional protein and has accumulated mutations that could be point mutations, indels, and gene duplication/amplification, could amplify, and the copies could then diverge to become two different types of proteins. An additional element influencing the evolutionary course of moonlighting proteins is the fitness benefits attained by each step (Jeffery, 2015).

The mutations that allow the bi or multifunctionality of a moonlighting protein may occur in the promoter region of a gene. Even a small change in the covalent structures of proteins can result in a protein's bifunctionality or in different functions in a protein. One of the examples is that post-translational modification can result in a switch between functions in moonlighting proteins. This type of modification can regulate the increase or decrease the rate of the enzyme's catalytic activity, or can be important in regulatory mechanisms for the bifunctionality of a protein that works in two different pathways. The post-translational modification can allow the proteins to transition that are reversible between their activities which also helps the cell to quickly adapt to the environmental changes.

A single amino acid mutation can also lead to the alteration or addition of a new function that results in a moonlighting protein. In some instances, the difference in protein function can be caused by differences in even less than 1% of the amino acid sequence. They are also called neomorphic moonlighting functions, which can cause several diseases by a single amino acid change, this is due to a mutation in a gene that there a new catalytic activity. Also, two protein species with homologous amino acid sequences usually share the same functions, but this is always not the case. Due to the small difference in amino acid sequence, two proteins may have different functions, and in moonlighting proteins, they may share both, one or no functions.

## IMPORTANCE OF MOONLIGHTING PROTEINS

### Moonlighting Proteins in Diseases

Moonlighting proteins have been discovered to play a significant role in diseases, like cancer, autoimmune disease, obesity, heart disease, and in diabetes. Some moonlighting proteins also play an important role in bacterial virulence, for example, Hsp70, glyceraldehyde-3-phosphate dehydrogenase (GAPD), enolase, and chaperonin 60 (Henderson and Martin, 2013). In breast cancer metastasis a moonlighting protein phosphoglucose isomerase plays an important role.

### Moonlighting proteins in system biology

As mentioned above, some moonlighting proteins function as a switch between two pathways and increase the cell's ability to adapt to various environmental changes, or they provide a mechanism to switch between two pathways in response to the environmental changes. For example, IRPs are in charge of posttranscriptional regulation and reacting to variations in the amount of iron in cells by binding to iron-responsive elements (IREs) (Banerjee *et al.*, 2007). Studies of the functions of moonlighting proteins can help in understanding how the proteins respond to changes in cells' surroundings and how they switch functions.

### Moonlighting proteins in medicine

One-third of the population is infected by *Mycobacterium tuberculosis,* which causes tuberculosis, a



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moonlighting protein ISG15 becomes a significant factor since people lacking this moonlighting protein are very susceptible to tuberculosis. Another moonlighting protein GAPDH is generally involved in normal mammalian physiology and is a novel autocrine protein that is involved in controlling blood clotting and platelet accumulation. Dihydrolipoamide dehydrogenase (DLD) is a critical enzyme for redox balance and metabolism, deficiency in this moonlighting protein may result in disorders in children such as hypotonia and metabolic disorders (Huberts and van der Klei, 2010). Moonlighting proteins play a key role in human reproduction and homoeostatic regulation. A molecular chaperone Immunoglobulin heavy-chain-binding protein (BiP) may lead to a cure for rheumatoid arthritis (Panayi and Corrigall, 2014). This proves that in the coming years, moonlighting proteins may have therapeutic uses.

**Conclusion**

Moonlighting proteins are a class of proteins that have been discovered in the last few decades and carry out two or more different biochemical or biophysical tasks that are physiologically significant. Gene fusions, a range of RNA splice variants, or pleiotropic effects do not cause these functionalities. Moonlighting proteins are crucial to biological systems and medicine. How this multifunctionality arises is also an important question, we have three possible explanations for these questions, and we'll continue to find more about these proteins as more moonlighting proteins are found Furthermore, the importance and applications of moonlighting proteins will rise with new findings.

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