Molecular assembly and function of human Androglobin, an unusually large chimeric hemoglobin – to start October 2019

Christine Desty Scholarship, fully-funded (Home/EU fees £4630 plus stipend of £15,009) for an MSc by Dissertation (MSD) in the School of Biological Sciences, University of Essex

Background

Androglobin is a novel hemoglobin, discovered in 2012[1]. The hemoglobin of the erythrocyte is one the most studied proteins in science, however androglobin is paradoxically one of the least studied and understood proteins of the hemoglobin superfamily.

Androglobin is expressed in low levels in the lungs and high levels in the testes and may be involved in male fertility and lung disease (motile cilia being a common theme). Androglobin has a highly unusual arrangement with a circularly-permuted globin domain at its center (i.e. the second half of the protein is expressed before the first half), split by a calmodulin-binding domain. This is preceded by calpain domains, however, much of the protein has no known correlation with protein sequences.

The structure of this complex multi-domain protein of 1667 residues (cf ~140 residues for canonical hemoglobins) is completely unknown outside of Essex: the lack of recombinant protein studies is reportedly due to the instability of the heme domain when expressed[2]. However, we have overcome the stability issue and characterized much of its heme function, including interaction with calmodulin. (For the molecular dynamics of a model heme domain structure see https://youtu.be/UAT7OtHvzSI). Thus, we are in a unique position to discover the fundamental properties of this protein. Through our initial research we believe that the protein has multiple functions related to calcium cell-signalling and nitric oxide regulation and is potentially important in the development of germ cells.

The project aim is to investigate the structural and functional aspects of the heme domain of androglobin and its interaction with other androglobin domains or external proteins such as calmodulin through various biochemical experiments designed through the molecular modelling. Conditions to generate crystal structures of the globin domain have so far eluded us, but the significant increase in spectra quality of the heme domain in the presence of calmodulin suggests that crystallizing the heme in the presence of other domains is likely to be successful. Additionally, the protein will be expressed in human cancer cell lines, either transiently or through stably transfected protein, for cell stress studies. The unusual structural arrangement of this novel androglobin protein and the presence of calpain, known to control key physiological processes, make this a stimulating project with implications in male fertility issue and potentially cancer research[3].

References

1. Hoogewijs *et al*. (2012) “Androglobin: a chimeric globin in metazoans that is preferentially expressed in Mammalian testes” *Mol. Biol. Evol.* (29)1105-14

2. Bracke *et al.* (2018) “Exploring three different expression systems for recombinant expression of globins: Escherichia coli, Pichia pastoris and Spodoptera frugiperda” *Anal. Biochem.* 543 62-70
3. Huang *et al.* (2014) “Androglobin knockdown inhibits growth of glioma cell lines” *Int J Clin Exp Pathol.* 7 2179–84.

Entry requirements and application procedures
Highly motivated applicants with, or expecting, a good degree in the broad area of Life Sciences are encouraged to apply.
Applications should be submitted electronically by **24th April 2019** see here for details https://www.essex.ac.uk/pgapply/enter.aspx

You are encouraged to contact the supervisor before application: reedb@essex.ac.uk and reync@essex.ac.ukIf you have any queries with the online application process, please contact ecrix@essex.ac.uk

For general information about the School of Biological Sciences at the University please visit our webpages http://www.essex.ac.uk/bs/.

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