
**Investigating the regulation of miRNA
biogenesis and Argonaute2 by RNA binding
proteins**

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Declaration

I declare that the work presented within this thesis is, unless stated otherwise, entirely my own; that all references cited herein have been consulted by myself; and that this work has not been previously accepted for a higher degree.

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I certify that Patrick Peter Connerty has carried out research under my supervision and has fulfilled the conditions of the relevant ordinance and regulation for the completion of a PhD degree.

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Gyorgy Hutvagner

25/6/2016

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Abstract:

microRNAs (miRNAs) are small non-coding RNAs which post-transcriptionally regulate gene expression. As miRNAs control many important biological processes it is important that their own production is highly controlled too. A range of auxiliary proteins involved in regulating miRNA biogenesis have been documented extensively, highlighting the complexity of the miRNA pathway. This study identifies novel roles of RNA binding proteins which are both canonical and auxiliary to the miRNA biogenesis pathway.

Here, we demonstrate that inhibition of p72 and KHSRP decreases Ago2 protein stability through disturbing miRNA biogenesis and therefore miRNA abundance. Furthermore, we have demonstrated that Ago2 is subject to multiple types of regulation as transient knockdown of Dicer stabilises Ago2 protein despite a decrease in miRNA abundance via an unknown mechanism.

Additionally, we have established that miRNA biogenesis is subject to a possible negative feedback mechanisms in which impairment of Dicer function both promotes and inhibits pri-miRNA production in a pri-miRNA and cell specific manner.

Finally, this study provides evidence to suggest that both mature miRNA levels and miRNA target abundance can stabilise miRNA biogenesis and promote pri-miRNA production in the absence of key and auxiliary proteins involved in miRNA biogenesis.