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A cancer piggy-back screen to investigate whether changes in epigenetic state drive cancer growth

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Abstract

Our group established an ENU mutagenesis to identify genes involved in epigenetic reprogramming. The screen utilizes a transgenic GFP reporter gene, which is expressed in a variegated manner in erythrocytes and is highly sensitive to epigenetic changes. A gene discovery pipeline involving whole exome sequencing aided in the rapid identification of causative mutations in ~40 lines. The screen has produced mouse mutants of both known modifiers of epigenetic state, such as *Dnmt1* and *Smarca5*, and genes not previously associated with regulation of epigenetic state e.g. *Smchd1* and *D14Abb1e*. The panel of mutants produced in the screen can be used as a tool to uncover the involvement of alterations in epigenetic state in both development and disease.

The epigenome is known to be severely disrupted in many cancer types. However, it is still not clear whether epigenetic changes drive cancer initiation or are a consequence of cancer growth. A secondary screen of *Momme* mice is being conducted to determine whether loss of specific epigenetic modifiers can alter cancer risk. In this system cause and effect are clear. Initial screening has identified ovarian teratomas in homozygous mutants carrying a *Foxo3A* mutation, sporadic growths in heterozygous mice for the chromatin remodeler *Pbrm1*, and sporadic ovarian growths in a third line in which the causative mutation is yet to be identified. Further work is being undertaken to characterize the molecular pathways involved in each case.

Biography

Dr. Sarah Harten, an NHMRC Early Career Research Fellow, undertook her doctoral studies at Imperial College London, investigating the role of the VHL/HIF pathway in renal cancer. In 2010 she returned to Australia to work with Professor Emma Whitelaw on a mouse mutagenesis screen to identify novel epigenetic modifiers. Using a combination of mouse models, molecular techniques and next generation sequencing technologies, Dr Harten hopes to uncover the mechanism of action of previously uncharacterized epigenetic modifiers and their contribution to both development and disease. Her team also investigates the involvement of alterations in epigenetic state to cancer initiation and growth.