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Germline/meiotic genes in cancer: new dimensions

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Intergenerational passage of genetic information in humans is dependent on a complex sexual program which is orchestrated by a large cohort of tissue-specific germline genes. These genes drive a range of germline-specific pathways including spermatogenesis in males and the reductional chromosome segregation of meiosis. In somatic tissues these genes are transcriptionally silenced, but can become activated in cancerous tissue.[1-3] Initial interest in these genes was driven by the need to identify new cancer-specific biomarkers that could be used for diagnostics, prognostics and/or immunotherapeutics, and the first group to be discovered became widely known as the cancer/testis antigen (CTA) genes as they were expressed only in the testis and cancerous tissues, but not in healthy somatic cells. Latterly, many of these gene have also been referred to as the cancer germline genes.[1,2]

Despite the early interest in these genes as clinical biomarkers or targets, recent works have started to reveal another important cancer-associated role, one which has undergone remarkably limited scrutiny. It has emerged from various studies that germline genes can contribute to oncogenesis and can also contribute to tumor maintenance and drug resistance,[1,2] potentially revealing this family of proteins as potent new drug targets.

The genes that drive and maintain the male germline have a range of distinct functional roles, including germline cell maintenance in mitotically proliferating spermatagonial cell populations, cellular differentiation during spermatogenesis and the chromosomal reduction of meiosis. To date, many of the CTA genes that have been identified are encoded by the X chromosome and their expression is restricted to the spermatagonial germline cells, becoming transcriptionally inactive during the differentiation to meiotic spermatocytes. A recent screen for new cancer germline genes based on the human orthologues of mouse meiotic spermatocyte genes revealed a large number of autosomally encoded cancer germline genes that were transcriptionally activated in a wide range of cancer types.[4,5] A number of these human genes have been shown to encode meiosis-specific functions, including the meiosis-specific inter sister chromatid cohesion protein gene *RAD21L* and the transcriptional activator / meiotic recombination hot spot regulator gene *PRDM9*.[4,5] From this, it was speculated that the activation of such genes could drive oncogenesis and tumor evolution by interfering with normal equational mitotic chromosome segregation programmes, thus driving oncogenic genome instability.[4,5] However, while germline genes have been implicated in a number of oncogenic processes, until recently no direct evidence had been offered to implicate meiosis-specific chromosome regulators in oncogenesis or tumor maintenance. This changed when it was discovered that the ALT telomere maintenance pathway used by some telomerase deficient cancer cells to maintain their telomeres was dependent upon 2 meiosis-specific factors, Hop2 and Mnd1, both of which normally drive the mechanism that biases meiotic recombination to establish the inter homolog connections required for correct reductional chromosome segregation during meiosis I.[6] This discovery adds a new class of factors to the complex mix of genes that become activated during oncogenesis and highlights the need to explore the functional activity of other human meiotic genes that may contribute to cancer formation, maintenance and evolution.[4,5] In addition, it places further importance on the study of basic molecular mechanisms of the meiotic program.

Remarkably, given the emerging importance of germline genes and meiosis-specific genes in cancer, very little is known about their transcriptional regulation. Some studies imply that many of these genes are under a similar regulatory pathway, so that when this becomes dysregulated, functionally related groups of genes become active driving inappropriate functional germline/meiotic modules.[3] The epigenetic regulation of previously well characterized CTA genes has been relatively well documented with all studied genes being controlled at some level by the methylation of DNA transcriptional regulatory regions. These genes are activated when cells are treated with the DNA methyltransferase inhibitor 5-AzaC. However, a new layer of complexity to this activation has been revealed by a recent study that demonstrated that not all human cancer germline genes are activated by inhibition of DNA methyltransferases, indicating a complex hierarchy of

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germline, and possibly meiotic, gene activation.[7] In this study it was shown that not only did some cancer germline genes fail to become activated upon inhibition of DNA methyltransferase activity, a number were only transiently silenced during exposure to the demethylating agents while others remained more robustly activated following removal of the demethylation agent.[7]

Altogether, the finding that meiosis-specific factors can contribute to oncogenesis and that the normal somatic silencing of germline genes is controlled by unique, as yet uncharted factors, makes the study of meiotic and germline genes in cancer an emerging and important field, one which impinges directly on a range of clinical applications including diagnostics, patient stratification/prognostics and new therapeutic and drug targeting strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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