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MDS Is a Stem Cell Disorder After All

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Myelodysplastic syndrome (MDS) has long been presumed to be a stem cell disorder, but rigorous formal proof has been lacking. In this issue of *Cancer Cell*, Woll and colleagues demonstrate that driver mutations occurring in MDS definitively occur in cells with a stem cell phenotype.

Myelodysplastic syndrome (MDS) is comprised of a heterogeneous set of disorders characterized by ineffective hematopoiesis, morphologic dysplasia of one or more hematopoietic lineages in the marrow, and progression to acute myeloid leukemia (AML) in some cases. Early evidence for a stem cell origin for these disorders was provided by clonal detection of skewed X chromosome inactivation patterns and the identification of characteristic chromosomal abnormalities in cells of multiple lineages from MDS patients (Gerritsen et al., 1992; Janssen et al., 1989); however, formal demonstration that MDS is a stem cell disorder at the genetic level has been limited (Nilsson et al., 2000).

A paradigm that has taken root in cancer biology over the last several years is the cancer stem cell hypothesis (Reya et al., 2001). This hypothesis states that cancer occurs by acquisition of genetic or epigenetic changes until the normal cell of origin has been phenotypically altered such that it is capable of fully propagating the tumor. In normal ontogeny, only true tissue stem cells possess life-long self-renewal potential; thus, driver mutations must occur in bona fide stem cells unless the mutations are able to directly confer this potential on committed progenitors. Evidence for the cancer stem cell hypothesis has largely been limited to tumor xenograft models, and direct demonstration of their existence in humans cancers has only come through recent studies that have attempted to identify genetic lesions in "preleukemic" stem cells from AML patients (Jan et al., 2012; Shlush et al., 2014).

The spectrum of driver mutations in MDS and the clinical impact has been revealed by high-throughput sequencing studies on large numbers of MDS samples (Bejar et al., 2011; Haferlach et al., 2014; Papaemmanuil et al., 2013). In this issue of *Cancer Cell*, Woll et al. (2014) utilize this knowledge to integrate cellular hierarchy with cancer genetics to show definitively that lesions implicated as driver mutations in MDS are present in hematopoietic stem cells (HSCs) as defined by phenotypic cell surface markers.

The experimental design is elegant in its simplicity. The authors reasoned that if the genetic lesions occurred in stem cells, they would be present in the cells expressing stem cell markers; however, if the lesions transformed committed progenitor cells that normally lack self-renewal potential, then the lesions would be absent in the stem cell compartment. They first demonstrated that cells in the phenotypically defined stem cell compartment from MDS patients are functional stem cells in xenograft assays. They then identified 34 somatic genetic lesions in 15 patient samples and demonstrated that all of these mutations were present in the stem cell compartment (Figure 1). There were no cases of mutations found in the bulk population of MDS cells that were not also present in stem cells.

The authors next sought to delineate how mutations were acquired during progression to AML in a subtype of MDS in which the inciting lesion is a loss of the long arm of chromosome 5 in stem cells

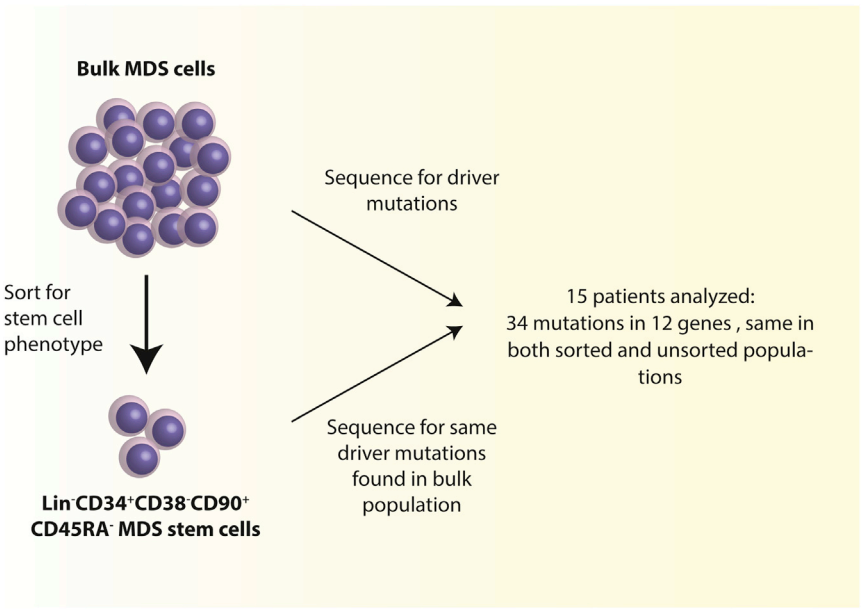

Figure 1. Driver Mutations Found in Bulk MDS Cells Are also Seen in MDS Stem Cells
Cells from MDS bone marrow were sorted by stem cell markers, and sequencing for driver mutations was performed on both unsorted and sorted populations. All of the mutations seen in sorted stem cells were identical to mutations in the bulk population.

(del(5q) MDS). In one patient who progressed to AML, all of the newly acquired mutations were detectable in the stem cell compartment. In a second patient with disease progression, one of the newly acquired mutations was detected in bulk cells from the advanced lesion, but not in the stem cell compartment, suggesting that it was acquired in a downstream progenitor that had acquired self-renewal potential. Thus, paths to leukemic transformation can occur either in stem cells or in progenitor cells.

These findings provide strong evidence that mutations occurring in phenotypically defined stem cells indeed drive the pathogenesis of MDS. However, several questions remain unanswered. The authors assume that mutations driving MDS occurred in stem cells because they found the mutations in cells defined by having a particular set of surface markers. Is it possible that acquisition of certain mutations in committed progenitors "reprograms" them to a stem cell phenotype, expressing the canonical HSC surface proteins? Which mutations must occur in stem cells, and which can confer self-renewal potential to committed progenitors? Larger data sets, along with functional experiments, will be needed to answer these questions.

It has been suggested that therapies eradicating the MDS stem cell are necessary for curing disease. However, the authors demonstrate that the stem and progenitor compartment in low/intermediate risk MDS is minimally perturbed, although the MDS clone has already taken over the marrow at the time of disease presentation. Might therapies that improve the functionality of the differentiated progeny be effective? Nonetheless, the work by Woll et al. (2014) does further demonstrate that MDS is indeed a stem cell disorder.

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GNAQ/11 Mutations in Uveal Melanoma: Is YAP the Key to Targeted Therapy?

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GNAQ **and** ***GNA11*** **are frequently mutated in uveal melanoma, but they remain difficult therapeutic targets. In this issue of** ***Cancer Cell*****, Feng and colleagues and Yu and colleagues demonstrate that the oncogenic activity of mutant GNAQ/11 is mediated at least in part through YAP, potentially uncovering a new therapeutic strategy.**

Malignant melanomas that arise from the iris, ciliary body, and choroid layers of the eye—collectively referred to as uveal melanomas—represent the most common primary cancer of the eye and the second most common form of melanoma (Harbour, 2012). Despite the availability of highly effective treatments for eradicating the primary tumor, up to half of affected individuals later develop metastatic disease that is almost always fatal within a few months. Until recently, the identification of effective therapies for metastatic uveal melanoma has been hampered by a lack of known driver mutations. This situation has changed in recent years with the discovery of several common driver mutations, which has opened the door to rational targeted therapies (Harbour, 2012).

Mutually exclusive mutations in the G protein-coupled receptor (GPCR) alpha subunits *GNAQ* and *GNA11* (encoding Gq and G11 proteins, respectively) are