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Review

Genomic instability, driver genes and cell selection: Projections from cancer to stem cells☆

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ABSTRACT

Cancer cells and stem cells share many traits, including a tendency towards genomic instability. Human cancers exhibit tumor-specific genomic aberrations, which often affect their malignancy and drug response. During their culture propagation, human pluripotent stem cells (hPSCs) also acquire characteristic genomic aberrations, which may have significant impact on their molecular and cellular phenotypes. These aberrations vary in size from single nucleotide alterations to copy number alterations to whole chromosome gains. A prominent challenge in both cancer and stem cell research is to identify "driver aberrations" that confer a selection advantage, and "driver genes" that underlie the recurrence of these aberrations. Following principles that are already well-established in cancer research, candidate driver genes have also been suggested in hPSCs. Experimental validation of the functional role of such candidates can uncover whether these are bona fide driver genes. The identification of driver genes may bring us closer to a mechanistic understanding of the genomic instability of stem cells. Guided by terminologies and methodologies commonly applied in cancer research, such understanding may have important ramifications for both stem cell and cancer biology. This article is part of a Special Issue entitled: Stress as a fundamental theme in cell plasticity.

1. Introduction

1.1. Human pluripotent stem cells (hPSCs) resemble cancer cells

Human pluripotent stem cells (hPSCs) can be derived by isolating the inner cell mass of embryos at the blastocyst stage [1], by transient induction of transcription factors in somatic cells [2], or through somatic cell nuclear transfer [3]. Regardless of their cellular origin, however, hPSCs are fundamentally different from their in-vivo counterparts: while maintaining the ability to differentiate into any cell type of the human body, hPSCs acquire in culture an extraordinary self-renewal and proliferation capacities, which do not exist at all in the pluripotent cells of the blastocyst.

Indeed, the only cells that exhibit a parallel proliferative capacity are cancer cells, and the relationship between these cell types has therefore been at the focus of extensive research (reviewed in [4]). In line with the notion that induced pluripotency and tumorigenic transformation are related processes [5], hPSCs share many hallmark characteristics with human cancer cells, including similar genomic [6,7] and epigenomic [8,9] landscapes, unique activation of some signal transduction pathways (e.g., [10]), high levels of telomerase activity [11] and lack of contact inhibition [1]. Undoubtedly, one of the most striking similarities between hPSCs and human cancer cells is their genomic instability [12]; both hPSCs and cancer cells are genomically unstable, and are prone to acquire genetic aberrations at the levels of whole chromosomes, sub-chromosomal loci or single genes (reviewed in [13–15]).

1.2. Genomic instability in cancer cells and in hPSCs

One of the most dramatic manifestations of cellular adaptation to a stressful environment is the stable acquisition of genomic aberrations. These alterations in the genomic material can range in size from a single base to an entire chromosome, and can consequently affect the expression of a single gene (in the case of a point mutation), of several genes (in the case of small gains and deletions), or even of thousands of genes simultaneously (in the case of aneuploidy). Unlike epigenetic changes, genetic changes are often irreversible, at least at the level of the single cell.

Both in cultures of hPSCs and in tumors, genomic aberrations initially lead to genomic variation, namely to a genetically-heterogeneous cell population [16–18]. However, under conditions that promote clonal selection, cells that harbor advantageous aberrations will soon outcompete their counterparts and thus give rise to the dominant, and often sole, surviving clone. Consistent with that, both human tumors and hPSC cultures eventually become clonal, and genomic aberrations that confer a selection advantage thus get fixed in the cell population [16, 17,19].

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While cells in culture may be inherently unstable, cancer cells and pluripotent cells proliferate much faster than normal mature cell types, and — importantly — they do not senesce in culture. Therefore, these cell types are more prone to acquire genomic abnormalities, and these abnormalities may significantly increase their in vivo tumorigenicity [4]. Other factors that may make these cell types particularly vulnerable to genomic insults include unique cell cycle characteristics and DNA damage repair mechanisms, as well as cell culture practices and culture conditions (reviewed in [15]).

1.3. Uncovering driver genes that underlie genomic aberrations

Multiple studies have recently described in detail the recurrent genomic aberrations in hPSCs (reviewed in [13,15]). However, the causes and consequences of these aberrations remained largely unexplored until recently. Presently, it seems that the focus of the field is gradually shifting from descriptive studies that identify and characterize the aberrations to mechanistic studies that aim to unravel their potential "consequences" on the one hand, and their "causes" on the other hand.

A key challenge pertaining to the "cause" of genomic aberrations is the identification of underlying genes that drive recurrent aberrations. Adopting cancer research terminology, this problem could be phrased in terms of "driver" and "passenger" aberrations/mutations: which aberrations and which genes confer a substantial selection advantage, and how can these genes be distinguished from innocent bystanders? There are actually two interwoven challenges here: first, the driver aberration(s) need to be identified on the noisy background of other present genomic changes; second, the key genes that underlie the driver aberration(s) (i.e., the driver genes) have to be determined, often on the background of many other genes that reside within the aberrant region. As in cancer, the global genomic instability that characterizes late-stage cultures of hPSCs may mask both the driver aberrations and the driver genes, thus making their identification a rather difficult task.

2. Levels of genomic instability in hPSCs

As already mentioned, the genomic aberrations in hPSCs range in size from single nucleotide alterations (SNAs), to small gains and deletions (also referred to as copy number alterations, or CNAs), to trisomies or monosomies of whole chromosomes (that is, aneuploidy). This distinction is not merely technical, for different types of aberrations may stem from distinct defective mechanisms. This distinction may also be useful for the attempt to tease out the driver genes underlying the recurrent aberrations. The recurrent genomic aberrations in hPSCs, and the candidate driver genes that underlie these aberrations, are listed in Table 1.

2.1. Aneuploidy in hPSCs

Large chromosomal aberrations are commonly present in cultures of hPSCs. Whereas these aberrations are presumed to arise randomly, giving rise to karyotypically heterogeneous cultures [18], only few of them prevail and eventually take over the culture. Over a third of the human embryonic stem cell cultures exhibit identical chromosomal aberrations in over 5% of the cells [20]; and more than 10% of the hPSC cultures harbor at least one large chromosomal aberration in the majority of the cell population [12,21,22].

There are several lines of evidence that argue for the positive selection involved in the accumulation of large chromosomal aberrations in hPSC cultures. First, some chromosomal aberrations are significantly more common than others: trisomies of chromosomes 1, 12, 17 and X (or gains of one of their arms) are much more prevalent in hPSC cultures than any other trisomy or monosomy [12,19–24]. Second, chromosomal aberrations often take over the culture very rapidly, so that very few passages can go by from their first detection in rare cells to their widespread existence in culture [19,21]. Third, it has been recently shown that the most common aberration in hPSCs, trisomy 12, induces profound changes in the global gene expression signature of hPSCs, increasing their proliferation rate and their tumorigenicity [25]. Fourth, the same chromosomal aberrations that arise in hPSC cultures also arise in germ cell tumors in-vivo [12,19]. Fifth, some of the recurrent chromosomal aberrations in hPSCs are also observed in the syntenic chromosomes of mouse and monkey PSCs, suggesting their evolutionary-conservation [26]. Lastly, the chromosomal aberrations that arise in hPSC cultures are strikingly different from those that arise in embryogenesis [27], highlighting the role of the stressful environment in supporting the specific aberrations observed in culture.

Considering that only few aneuploidies facilitate the survival of hPSCs and allow them to prevail, a key question for each of these common aberrations is which gene(s) endow the cells with a selection advantage. As hPSCs acquire mainly trisomies, one would expect the driver genes to be over-expressed in the aneuploid cells. However, as large chromosomal aberrations encompass hundreds — and even thousands — of genes, it is difficult to determine which ones are the driver genes. It has been shown that 20%–40% of the genes within an aberrant region are significantly differentially expressed [21]; pinpointing one or few genes that are not only over-expressed in a trisomy, but are also essential for its accumulation, is therefore highly challenging. Nonetheless, as will be described below, application of several approaches has

Table 1
A list of recurrent genomic aberrations in hPSCs, and the candidate driver genes underlying these aberrations.

Key publication(s)	Supportive evidence or validation(s)	Proposed selection advantage	Candidate gene(s)	Recurrent genomic aberration
[20,21,29,52]	Consistent over-expression in aberrant cells Over-expression of *NANOG* jeopardizes differentiation Known role in cancer	Promoting self-renewal	*NANOG* *NANOGP1* *GDF3*	Trisomy 12 / Gain of 12p / Gain of 12p13.31
[19,26,55,56]	Over-expressed in aberrant cells Evolutionarily-conserved aberration Essential for the viability of hPSCs and for tumor formation Known role in cancer	Inhibiting apoptosis	*BIRC5* (*Survivin*)	Trisomy 17 / Gain of 17q
[26]	Over-expressed in aberrant cells Evolutionarily-conserved aberration Known role in cancer	Unknown	*ICT1*	
[20,31,32]	Over-expressed in aberrant cells Known role in cancer Direct evidence from knockdown and over-expression experiments	Inhibiting apoptosis	*BCL2L1* (*BCL-XL* isoform)	Gain of 20q11.21
[19]	–	Progressing cell cycle	Androgen receptor (*AR*)	Trisomy X