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Centrosome amplification and clonal evolution in multiple myeloma: Short review

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ABSTRACT

Multiple myeloma (MM) is composed of an array of multiple clones, each potentially associated with different clinical behavior. Previous studies focused on clinical implication of centrosome amplification (CA) in MM show contradictory results. It seems that the role of CA as well as CA formation in MM differ from other malignancies. This has brought about a question about the role of CA positive clone which is—is it going to be a more aggressive clone evolutionally arising under pressure of negative conditions or can CA serve as a marker of cell abnormality and lead to cell death and further elimination of this damaged subpopulation?

This current review is devoted to the discussion of the existence of MM subclones with centrosome amplification (CA), its evolutionary behaviour within intraclonal heterogeneity as well as its potential impact on the disease progression and MM treatment.

1. Introduction

Cancer is frequently considered to be a disease of cell cycle. Indeed, this is a complex multistep process, which results from dynamic reprogramming of the genome and leads to autonomous cell behavior, including uncontrolled proliferation.

Historical knowledge of heterogeneity in cancer, both from a histopathological and genetic perspective coupled with a large number of recent studies document extensive intratumoral genetic heterogeneity in a wide range of malignancies including monoclonal gammopathies (Lengauer et al., 1998; Swanton, 2012; Burrell and Swanton, 2014a). Briefly, heterogeneity occurs first at the cellular level (intercellular heterogeneity) but with selective outgrowth of any given cell clone, varying degrees of clonal heterogeneity may arise. Subclones may expand and evolve in a sequential linear fashion, or otherwise may continue to diverge, following branched evolutionary trajectories (Burrell and Swanton, 2014b).

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Multiple myeloma (MM) is composed of an array of multiple clones, each potentially associated with different clinical behavior. Some clones will be more proliferative and associated with rapid clinical progression and early relapse, while others may be less proliferative or even out of cycle and associated with late relapse (Morgan et al., 2012). These cellular fractions are heterogeneous in their mutational and chromosomal makeup as well as biological features that determine the variability in tumor progression, clinical aggressiveness and sensitivity to therapy seen in cancer (Melchor et al., 2014). The current review is devoted to the discussion of the existence of MM subclones with centrosome amplification (CA), its evolutionary behaviour within intraclonal heterogeneity as well as its potential impact on the disease progression and MM treatment.

2. Centrosome amplification in multiple myeloma

2.1. Centrosome amplification is a concomitant event of uncontrolled proliferation, but not in multiple myeloma?

Centrosomes are small cell organelles composed of two cylindrically shaped centrioles surrounded by pericentriolar material in a normal mitotic cell. The centrosome function is to direct mitotic bipolar spindles in a process that is essential for accurate chromosome segregation during mitosis (Hinchcliffe and Sluder, 2001; Kramer et al., 2002). Centrosomes duplicate once per cell cycle and each daughter cell receives one centrosome upon cytokinesis (Rebacz et al., 2007).

Centrosome dysfunction is particularly prevalent in tumors in which the genome has undergone extensive structural rearrangements and chromosome domain reshuffling (Pihan, 2013). It is now well established that centrosome abnormalities in cancer correlate closely with chromosome instability (CIN) (Pihan et al., 1998). However, correlative evidence does not establish causality. Conversely, there is evidence that centrosome contributes to cell-cycle regulation and checkpoints (Wang et al., 2009; Mikule et al., 2007). These observations place centrosome abnormalities at the earliest stages of cancer development (Pihan, 2013). Nevertheless, despite their common occurrence, and perhaps due to the heterogeneity of centrosome abnormalities in cancer, it has been difficult to determine the origin of centrosome abnormality, whether centrosome abnormalities are caused by primary intrinsic centrosome defects, or are the consequence of dysfunction of other cellular processes that lead to the accumulation of normally replicated centrosomes (Nigg, 2002; Storchova and Pellman, 2004). At present, centrosome abnormalities have become very alluring investigative targets in the prospects of utilizing these defects as biomarkers and targets for cancer specific therapy.

Most cells in adult organisms do not divide and are maintained at a post-mitotic stage, which is also known as quiescence. Since one of the fundamental hallmarks of all cancer process is uncontrolled proliferation (Hanahan and Weinberg, 2000; Hanahan and Weinberg, 2011), then a question arises, if tumors often originate from adult tissues in which most cells are quiescent, how do tumor cells undergo uncontrolled proliferation? Thus, the proliferative advantage of tumor cells or certain tumor clones arises from their ability to bypass quiescence. This question is very relevant for myeloma cells when taking into consideration that primary plasma cells are terminally differentiated and no longer divide—they are arrested in the G1 phase of cell cycle as intermediates in plasma-cell differentiation, which is a consequence of transformation (Tourigny et al., 2002). Centrosome amplification as well as aneuploidy represents the concomitant events of uncontrolled proliferation in carcinogenesis. In spite of this, unlike other tumors, proliferation index in MM is predominantly low and chromosomal instability and supernumerary centrosomes are the typical feature of multiple myeloma. Moreover, they represent an early event in myeloma genesis (Chng et al., 2006a).

2.2. Centrosome amplification in MM: is it a good sign or a bad omen?

There is a question that arises about the role of CA positive clone—is it going to be a more aggressive clone evolutionally arising under pressure of negative conditions or can CA lead to cell death and further elimination of this damaged subpopulation?

It was shown by Sato et al. (2000) that centrosome overduplication may be a critical event that leads to mitotic failure and subsequent cell death following crucially damaging influence and that it represents a mechanism that defends organisms from abnormal cell accumulation.

This suggestion seems logical, considering that dysfunctional or supernumerary centrosomes will either impede cell division or cause multipolar divisions, which most frequently lead to mitotic catastrophe. Neither of these phenotypes would be expected to favour the clonal expansion of a tumor cell (Nigg, 2002). In our opinion, the same statement should coincide with aneuploidy and chromosomal instability should be initially detrimental towards tumor development. The frequent aneuploidy observed in human tumors may remain in some cases as a fingerprint of original "oncogene-induced mitotic stress" chromosomal instability, generated by loss of tumor suppressors (Malumbres, 2011). Analyses of human tumors have revealed a strong positive correlation between centrosomal abnormalities and aneuploidy, which has been frequently used to support a possible causal role of chromosomal instability in tumor formation. However, anti-proliferative effect of aneuploidy still leaves an open question of the function of aneuploidy, if it is oncogenic or tumor suppressive (Holland and Cleveland, 2009; Nicholson and Cimini, 2015). Thus, mitoses with multipolar spindles are inherently inefficient, exhibiting a high rate of intramitotic (mitotic catastrophe) (Vitale et al., 2011; Castedo et al., 2004; Vakifahmetoglu et al., 2008), post-mitotic cell death (Varmark et al., 2009), or senescence (Andreassen et al., 2001), hindering tumor growth and acting as tumor suppressors rather than tumor promoters (Ganem et al., 2009; Weaver and Cleveland, 2007; Weaver et al., 2007).

In our previous study, we showed that a better 2-years overall survival (OS) was indicated for newly diagnosed patients with apparent CA positive clone. In addition, CA as a prognostic factor was relevant for disease-related death cases that occurred within two years after diagnosis (Dementyeva et al., 2013). Presumably, these findings could be explained according to the assumption that mitotic aberrations associated with numerical and functional abnormalities of centrosomes trigger spindle checkpoints, leading to mitotic catastrophe and cell death (Fukasawa, 2007). In these cells with CA, the threshold of apoptosis activation induced by drugs (Lee et al., 2010) or radiation (Saito et al., 2008) may be much lower. Illusive contradiction with findings of Chng et al. was discussed in our previous publication (Dementyeva et al., 2013).

2.3. Centrosome amplification in MM: proliferation activity and apoptotic puzzle

Importantly, in those tumor types where CIN is present, there is a significant correlation between the CIN phenotype and poor prognosis (Pinto et al., 2015; Hveem et al., 2014), which suggests that chromosome imbalance might specifically contribute to aggressive or metastatic cancer (Carter et al., 2006; Perez de Castro et al., 2007). However, in the case of multiple myeloma, hyperdiploid-type is associated with better survival compared to nonhyperdiploid-MM (Chng et al., 2006b). We are inclined to think that such statements