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Review paper

c-Myc MISREGULATION TRIGGERS COMPLEX PROCESS OF GENOMIC INSTABILITY

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Genetic stability is an essential factor for the cellular integrity. Failure in its maintenance leads to accumulation of errors derived from the process of DNA replication, cellular metabolism, action of endogenous and exogenous DNA damaging factors and eventually, as a final outcome tumor initiation and progression occur. Overall manifestation of *c-Myc* deregulation in many tumors and different mechanisms of Myc's action toward genomic stability suggest that this gene plays a central role in destabilization of genome. Microarray studies and functional genomics approach led us to conclusion that c-Myc can control nuclear architecture in global fashion since about 15% of all cellular genes are regulated by this transcription factor. Deregulation of *c-Myc* gene triggers a composite network of genomic instability that may result in several different outcomes as: locus-specific amplification, formation of extrachromosomal elements (EEs), chromosomal instability, long-range illegitimate recombination, point mutations, DNA breakage and nuclear structure reorganization. This review outlines the growing evidence that *c-Myc* oncogene induces a complex network of genomic instability and describes systems and circumstances under which deregulation of *c-Myc* results in specific types of genomic alteration.

Keywords: *c-Myc*, genomic instability, DNA damage, chromosomal rearrangement, gene amplification.

INTRODUCTION

The human *myc* gene family consists of three members: *c-Myc* oncogene (*Myc* oncogene), *L-Myc* and *N-Myc*. The *c-myc* and *N-myc* genes hold a three-exon organization with a

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main coding domain positioned within exons 2 and 3 (BATTEY *et al.*, 1983; DEPINHO *et al.*, 1986; KOHL *et al.*, 1986; STANTON *et al.*, 1986). Amplified *N-myc* gene was identified mostly in human neuroblastomas, while the role of *L-Myc* is less understood (DANG, 2012). The *c-Myc* is expressed in most developing tissues at considerable levels, whereas *N-Myc* and *L-myc* expression are restricted to limited types of tissues during some developmental stages (DEPINHO *et al.*, 1987; DEPINHO *et al.*, 1986; HIRVONEN *et al.*, 1991; JAKOBOVITS *et al.*, 1985; LANG *et al.*, 1988). The protein coded by c-*Myc* oncogene represent a bHLHZip transcription factor that is conserved during evolution from *Xenopus* to *Homo sapiens* (THOMPSON, 1998). A large-scale screen using bioinformatical approach estimated about 11% of all cellular loci as potential Myc-binding sites (FERNANDEZ *et al.*, 2003).

Nowadays it is clear that c-Myc plays significant role in cell growth control, regulation of translation initiation, embryonic vascular permeability and remodeling, metabolism of normal and cancer cells, apoptosis, and hematopoiesis (EVAN and LITTLEWOOD 1993; KOKAI *et al.*, 2009; SCHMIDT, 2004; STINE *et al.*, 2015; THOMPSON, 1998). Misregulation of *c-Myc* oncogene is detected in a wide variety of human and animal tumors comprising: myeloid and lymphoid neoplasias; breast cancer; bowel cancer; colon cancer; small cell lung carcinomas; and glioblastomas (DELGADO *et al.*, 2013; GUILLEM *et al.*, 1990; HAN *et al.*, 2012; HERMS *et al.*, 1999; LIAO and DICKSON, 2000; MARINKOVIC *et al.*, 2004b; PRINS *et al.*, 1993; ROTHBERG, 1987). Regardless of extensive scientific examination performed since the identification of *c–Myc* as an oncogene, single pathway that fully clarifies its role in tumor initiation and promotion has not been determined until today. Moreover, most of the research evidence implies contribution of multiple pathways in *c-Myc* dependent tumorigenesis, among which c-Myc induced genomic instability, may have a significant role.

Genetic stability is an essential factor for the cellular integrity, and failure in its maintenance leads to accumulation of errors derived from the process of DNA replication, cellular metabolism, and action of endogenous and exogenous DNA damaging factors (DONLEY and THAYER, 2013; FRIEDBERG *et al.*, 2004; LUOTO *et al.*, 2013; TUBBS and NUSSENZWEIG, 2017). Because of genomic instability, affected cells demonstrate shorter cell cycling and additional advantage of bypassing immunological control systems (YAO and DAI, 2014). Cell transformation and tumor development occur as a final consequence of this process. Genetically speaking, cancer results from impairment of genes known as oncogenes (genes that have potential to cause cancer), and impairment of tumor suppressor genes (genes that protect cells from carcinogenesis) (LODISH *et al.*, 2000). Since acquired genomic alteration inside normal cells results in tumor initiation and progression, and subsequent selection of more aggressive sub-clones (NOWELL, 1976), much of the effort has been directed toward the understanding phenomenon of genomic instability.

The term genomic instability, also used as genome instability and genetic instability, is widely used in literature to describe overall increased tendency of genome alteration during cell division. Genomic instability encompasses small (from one up to several nucleotides) and significant (chromosomal) structure variations named structural genomic instabilities, and variations in chromosome copies known as numerical genomic instabilities. Structural genomic instabilities involve DNA alterations known as substitutions, deletions, insertions, inversions, and translocations. Numerical genomic instabilities reflect deviations from diploid normal state (somatic cell contains two copies of chromosome) to nullisomy (absence of chromosome), monosomy (single copy of certain chromosome), trisomy (presence of three copies of certain

chromosome), and other polysomies (presence of multiple copies of certain chromosome) (MARINKOVIĆ and MARINKOVIĆ, 2012). The simultaneous presence of structural and numerical aberrations within the same single cell as result of combined structural and numerical genomic instability is labeled as karyotypic or chromosomal instability (MAI *et al.*, 2005).

This review outlines the growing evidence that *c-Myc* oncogene induces a complex network of genomic instability. We described systems and circumstances under which deregulation of *c-Myc* results in specific types of genomic alteration. Proposals of the potential mechanisms by which *c-Myc* triggers genomic instability, as a prerequisite for cellular transformation, were also discussed in the paper.

THE EFFECTS OF *c-Myc* MISREGULATION ON GENOMIC STABILITY

Determination of *c-Myc* gene as transformation-initiating human oncogene is tightly related to the phenomenon of genomic instability. Burkitt lymphomas were the first human tumors in which deregulated c-Myc expression was observed (ERIKSON *et al.*, 1983). These B cell lymphomas are associated with constitutive expression of *c-Myc* as result of balanced chromosomal translocation that juxtaposed *c-Myc* gene to strong enhancers of the Ig-encoding genes (DALLA-FAVERA *et al.*, 1982; MANOLOV and MANOLOVA, 1972). Obviously, in this case disturbance of genomic stability led through chromosomal translocation to constitutive c-Myc expression and introduction of the neoplastic process. The role of *c-Myc* in cell transformation was further confirmed with the establishment of the first c-Myc dependent mouse model of lymphoma (ADAMS *et al.*, 1985). Since c-Myc induced murine lymphomas regressed upon inactivation of this gene (KARLSSON *et al.*, 2003b), unless some additional genomic alterations occurred, it became evident that c-Myc triggered genomic instability contributes to carcinogenesis.

Deregulation of *c-Myc* gene triggers a composite network of genomic instability that may result in several different outcomes as: locus-specific amplification, formation of extrachromosomal elements (EEs), chromosomal instability, long-range illegitimate recombination, point mutations, DNA breakage and nuclear structure reorganization (MAI *et al.* 2005).

Locus specific-amplification

Gene amplification is an increase in a copy number of a certain gene without a proportional increase in other genes. Dihydrofolate reductase (*DHFR*) gene that code enzyme which reduces dihydrofolic acid to tetrahydrofolic acid was the first cellular gene whose amplification is linked to genomic instability induced by *c-Myc* (DENIS *et al.*, 1991). *DHFR* is found amplified in different cell lines that derive from hamster, mouse, and human, within 72 hours of inducible c-Myc deregulation (MAI *et al.*, 1996b). Nevertheless, amplification of *DHFR* was detectable only when c-Myc protein levels were upregulated. Subsequently, using mouse plasmacytoma model of c-Myc-dependent tumorigenesis, c-Myc-dependent amplification of the *DHFR* gene was demonstrated in vivo (POTTER and WIENER, 1992; TAYLOR and MAI, 1998). *DHFR* gene amplification induced by elevated level of c-Myc was detected also in human preinvasive cervical cancer and in intraepithelial lesions and cancer of cervix (ARVANITIS and SPANDIDOS, 2008; GUIJON *et al.*, 2007). Described *DHFR* gene amplifications were detected within the chromosome (intra-chromosomally) and on extra-chromosomal elements (EEs).

Over the last 20 years, scientific investigation identified a number of genes that loose stability and amplify as consequence of *c-Myc* deregulation, and the list is still growing. These genes were amplified intra-chromosomally and extra-chromosomally within 72 hours as a result of single induced misregulation of *c-Myc* (KUZYK and MAI, 2014). The list of amplified genes comprise: carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD) gene (CHERNOVA *et al.*, 1998), ornithine decarboxylase (GEORGE *et al.*, 1996), ribonucleotide reductase R2 gene (KUSCHAK *et al.*, 2002), cycline B1 and cycline D2 (MAI *et al.*, 1999). Amplification of these genes correlates with proliferation advantage, resistance to some cytotoxic drugs and with metastatic potential of the cell (KUZYK and MAI, 2014). Presented list of genes amplified due to misregulation of *c-Myc*, only contain targets that are examined in this context, therefore additional targets are expected to be discovered.

Besides amplification of particular genes, c-Myc induced locus specific-amplification may result in tumor-specific palindrome formation that includes inverted repeats and Myc binding sites (NEIMAN *et al.*, 2008; NEIMAN *et al.*, 2006). The large DNA palindrome formation is initiated by chromosome breaks at the molecular level. According to Tanaka et al. the position of palindromes in the genome of the cancer cell functions as a structural platform that maintenances consequent gene amplification (TANAKA *et al.*, 2006).

At present, there is a general consideration that c-Myc modifies stability of multiple genes and genomic sites through noncoding RNAs and microRNAs (miRNA) (HUPPI *et al.*, 2008). Computational analysis and experimental verification of the genomic sequence covering the PVT1 locus recognized 7 miRNAs. This locus is recognized as a cluster of T(2;8) and T(8;22) "variant" MYC-activating chromosomal translocation in about 20% of Burkitt's lymphoma. The miRNA labelled as hsa-miR-1204 was found to be present in high copy number in MYC/PVT1-amplified tumors, while all the miRNA precursor transcripts were expressed at higher levels in late-stage B cells. miRNA may be related with fragile sites and cancer-associated genomic regions (MORISHITA and MASAKI, 2015; ROSSI *et al.*, 2008).

Extrachromosomal elements formation

Extrachromosomal elements (EEs) are small circular DNA elements with repetitive motifs (GAUBATZ, 1990). They are found in all organisms with variability in size, sequence complexity and copy number. The fact that EEs contain sequences homologous to chromosomal DNA implies that they might derive from genetic rearrangements, such as homologous recombination. Cancer cells often carry different types of EEs. Some of these EEs from cancer cells are quite large, they are able to self-replicate and they contain sequences of complete cellular genes. EEs from cancer cells induced by c-Myc deregulation may be classified as some kind of episomes since they have ability to replicate, they carry Myc target genes and are transcriptionally competent (SMITH *et al.*, 2003).

Using scanning electron microscopy (SEM) Smith and associates examined extra-chromosomal elements isolated from MycER-activated Pre-B+ cells. (SMITH *et al.*, 2003). They found these EEs about 10 times larger comparing to extra-chromosomal elements isolated from non-MycER-activated control Pre-B- cells. Their generation took place through mechanisms of illegitimate replication, DNA breakage and DNA recombination. Interestingly, large c-Myc induced extra-chromosomal elements carry histones that are able to replicate, allowing them to behave as autonomous functional genetic units (SMITH *et al.*, 2003). Wiener and associates determined that in some plasmacytoma, c-Myc expression is acquired by an alternative mechanism linked to

EEs. They found that DCPC21 plasmacytoma carry *c-Myc* and *IgH* genes on extrachromosomal elements from which *c-Myc* is transcribed thus driving process of neoplasticity (WIENER *et al.*, 1999). Occurrence of the transcription-associated phosphorylation of histone H3 on the extrachromosomal elements further supports transcriptional activity of these EEs.

Chromosomal instability

Misregulation of *c-Myc* promotes an overall induction of chromosomal instability both, in vitro and in vivo. Chromosomal alterations besides formation of EEs include: centromere and telomere fusions, chromosome and chromatid breaks, formation of ring chromosomes, translocations, deletions, inversions, aneuploidy and the formation of Robertsonian chromosomes (KUZYK and MAI, 2014).

In one of the in vitro studies potential chromosomal instability was investigated in cell line that allow regulation of c-Myc protein level, Rat1A-MycER cells (MAI *et al.*, 1996a). Upon prolonged periods of MycER activation these cells displayed irreversible chromosomal aberrations such as: chromosome breakage, formation of circular chromosomal structures, chromosome fusions, extrachromosomal element formation and numerical changes. Interestingly, even transient excess of MYC activity increased tumorigenicity of Rat1A cells injected in nude mice, by at least 50-fold, as has been shown in a study performed in vivo by FELSHER and BISHOP (1999). The transitory excess of *c-MYC* activity in the Rat1A cells transferred into nude mice was followed by evident genomic instability, including chromosomal abnormalities, gene amplification, and hypersensitivity to DNA-damaging agents.

Long-range illegitimate recombination

Double strand breaks followed by illegitimate recombination are standard mechanism for chromosomal translocations. Rockwood and associates used model of lambda-MYC-induced mouse Burkitt lymphoma to study mutagenesis and genomic instability associated with c-Myc deregulation (ROCKWOOD *et al.*, 2002). They showed a clear difference in the type of genomic alteration between normal tissue and lymphomas. While 75% of the mutations in normal tissues were point mutations, in lymphomas about 65% genomic alterations were translocations, deletions and inversions. According to this research, genomic instability in mouse Burkitt lymphoma was characterized by a dominance of illegitimate genetic rearrangements that involved many different chromosomes. The same group of researchers further investigated the precise structure of lacZ/mouse rearrangements from lambda-MYC lymphomas and G6PD knockout mice by sequencing breakpoint junctions and defining the source of recombining mouse sequences (ROCKWOOD *et al.*, 2004). The structure of rearrangements from both systems were remarkably similar, which is consistent with the hypothesis that these recombination result from the mechanism of mutagenic repair of DNA double strand breaks, as a consequence of oxidative damage.

PROSPECTIVE MECHANISMS FOR *c-Myc* INDUCED GENOMIC INSTABILITY

How *c-Myc* intermediates network of genomic instability is still a question without a definitive and clear answer. *c-Myc* may disturb genomic stability through several potential mechanisms as: induction of illegitimate replication, DNA damage, stress-induced pathway and remodeling of nuclear architecture (KUZYK and MAI 2014; MAI *et al.*, 2005). None of these

mechanisms is enough to explain c-Myc induced genomic instability per se, but evidently, hey all have a certain contribution to this process.

c-Myc induces illegitimate replications

c-Myc plays a direct role in the control of DNA replication via interaction with the pre-replicative complex and localization to early sites of DNA synthesis. Increased expression of c-Myc causes higher replication origin activity with subsequent DNA damage and checkpoint activation (DOMINGUEZ-SOLA *et al.*, 2007). Several studies showed that c-Myc deregulation might lead to DNA endoreduplication and polyploidy (GANDARILLAS *et al.*, 2000; LI and DANG, 1999).

Replication-driven and segregation-driven amplification of genes are two basic mechanisms of gene amplification that dominate the literature (MAI *et al.*, 2005). According to replication driven mechanism, re-replication of specific gene happens within a single cell cycle. This model clarifies creation of intra-chromosomal amplification, but also the creation of extra-chromosomal amplification through release from chromosome by process of recombination. The segregation driven mechanism involves a chain of events that include DNA breakage, crossing-over, recombination and rejoining (MAI *et al.*, 2005). Some genes are deleted from their chromosomes during the segregation driven process and then they become parts of the extrachromosomal elements, episomes or double minutes (CARROLL *et al.*, 1988; MORRIS and THACKER, 1993). Both mechanisms might be involved in c-Myc induced gene amplification.

Ribonucleotide reductase R2 gene is amplified in mouse pre-B cell line as a result of c-Myc deregulation through replication driven mechanism (KUSCHAK *et al.*, 1999). Kushak and associates demonstrated that c-Myc promotes illegitimate DNA replication that results in more than one replication firing per origin per cell cycle. The same group of authors reported that c-Myc induces initiation of several rounds of replication of ribonucleotide reductase R2 gene within a single cell cycle (KUSCHAK *et al.*, 2002). In their experimental settings c-Myc forced 3-4 replication initiation forks on both alleles, thus acting as an illegitimate replication-licensing factor (KUSCHAK *et al.*, 2002). Myc dependent gene amplification through replication-dependent mechanism was demonstrated also for some other Myc's target as DHFR and Cyclin D2 gene (KUZYK and MAI, 2014).

c-Myc mediates formation of reactive oxygen species (ROS) that induce DNA damage

VAFA *et al* provided evidence that *c-Myc* oncogene activation may induce DNA damage and even bypass damage controls, thereby accelerating tumorigenesis via genetic instability (VAFA *et al.*, 2002). They described that short-term *c-Myc* activation can induce DNA damage prior to S phase in normal human fibroblast cells. Detected DNA damage correlates with increased formation of reactive oxygen species. Moreover, cells characterized by elevated ROS production escaped process of apoptosis. Therefore, the authors concluded that c-Myc mediates formation of ROS, which in turn induce DNA breakage. VAFA *et al.*, (2002) further implicated that increase in ROS production could be the consequence of a biochemical disparity that is triggered by the rapid boost in target gene products mediated by transcriptional activation of c-Myc.

What would be the consequences of DNA breaks induced by elevated formation of reactive oxygen species? Single double-strand DNA break could be sufficient to disturb genetic stability of the cell and to cause gene amplification, deletions and rearrangements (PIPIRAS *et al.*,

1998); loss of heterozygosity (MOYNAHAN and JASIN, 1997); and translocations (RICHARDSON and JASIN, 2000). Furthermore, extrachromosomal elements are also result of DNA breaks, illegitimate replication and recombination (SMITH *et al.*, 2003).

In the quest for Myc's target genes that are involved in production and control of ROS, in vitro *c-Myc* inducible systems were used. It has been detected that Myc prompts expression of mitochondrial gene *TFAM* (mitochondrial transcription factor A) that plays a role in mitochondrial biogenesis. *TFAM* regulates production of mitochondrial reactive oxygen species and therefore has a role in promotion of genomic instability (DANG *et al.* 2005). Besides *TFAM* another target gene of c-Myc, mitochondrial gene *PRDX3*, has been linked to production of reactive oxygen species (WONSEY *et al.*, 2002). PRDX3 encodes a mitochondrial protein of the peroxiredoxin gene family, a scavenger of reactive oxygen species, whose expression is induced by the elevated Myc protein level and it is reduced in c-Myc knockout cells. It has been demonstrated that PRDX3 is a bonafide Myc-target gene, with functional Myc-binding site, as demonstrated by Chromatin immunoprecipitation analysis (WONSEY *et al.*, 2002). However, it has also been demonstrated that peroxiredoxin 1 interacts with a region of the c-Myc transcriptional regulatory domain that is essential for transformation, leading to the inhibition of c-Myc-mediated transformation, (EGLER *et al.*, 2005). The role of *PRDX3* is to sustain mitochondrial mass and membrane potential in transformed rat and human cells, therefore it has crucial role in maintaining vital mitochondrial functions. In line with the implicated tumor suppressor role for Prdx1, erythrocytes and embryonic fibroblasts from prdx1-/- (peroxiredoxin 1, Prdx1) mice demonstrate c-Myc activation and elevated levels of ROS, followed by development of age-dependent hemolytic anemias and/or malignancies (EGLER *et al.*, 2005). We require further work in this field to fully understand the relationship between Myc and its target PRDX3.

Not surprisingly, there is experimental evidence that DNA breaks may occur due to c-Myc overexpression even via ROS independent mechanism. In their study, Ray et al. proved that MYC could induce DNA breaks, both in vitro and in vivo, autonomous of reactive oxygen species formation (RAY *et al.*, 2006). The authors observed formation of double-strand breaks upon c-Myc induction that are independent of reactive oxygen species production. ROS independent double-strand breaks were observed both in normal human fibroblasts cultured in 10% serum, as well as in murine lymphocytes in vivo. On the other hand, the authors detected ROS dependent double-strand breaks in normal human fibroblasts cultured in 0.05% serum. Therefore, they concluded that overexpression of MYC may trigger ROS and single-strand breaks under certain conditions, but mostly induces widespread double-strand breaks in vivo and in vitro, by mechanisms independent of reactive oxygen species production. Besides, elevated expression of c-Myc disturbs the repair of double-strand DNA breaks, causing an increase in chromosomal breaks and translocations (KARLSSON *et al.*, 2003a). Karlsson and associates described that in normal human cells, c-Myc overexpression even within one cell division cycle, results in a several-magnitude rise in the frequency of chromosomal breaks and translocations.

c-Myc bypasses pro-apoptotic effects of p53

Tumor suppressor gene *p53* plays important role in the regulation of cell cycling and gene amplification. *P53-/-* cells fail to arrest from cell cycle progression and significantly increase ability to amplify genes (LIVINGSTONE *et al.*, 1992; YIN *et al.*, 1992). *p53* gene also has important role in cellular responses to different types of DNA damage (KASTAN *et al.*, 1991).

Importantly, *p53* is linked to *c-Myc* since Myc signaling via the *ARF* tumor suppressor gene regulates *p53*-dependent apoptosis and immortalization of the cell (ZINDY *et al.*, 1998).
Generally, DNA damage is strong inducer of tumor suppressor p53 activity that leads to apoptosis of the cell thus preventing it from transformation. Despite the fact that overexpression of c-Myc in the cell induce DNA breakage, it seems that *c-Myc* oncogene triggers genomic instability that bypass pro-apoptotic effect of the p53 (VAFA *et al.*, 2002). c-Myc induced downregulation of p53 might be a possible explanation for described phenomenon (MAI *et al.*, 2005). Besides p53, c-Myc also interacts with other regulators of apoptosis. For example, upregulated c-Myc sensitizes cells to NF-kappaB- mediated apoptosis, therefore inactivity of NF-kappaB signaling is a requirement for Myc-induced carcinogenesis (KLAPPROTH *et al.*, 2009; SCHLEE *et al.*, 2007).

Although it may sound absurd, it seems that too much genomic instability prevents tumorigenesis, most probably by inducing process of apoptosis (ATTARDI, 2005; NELSON *et al.*, 2004). This view was confirmed by the experimental observation that aneuploidy might act as both tumor promotion and tumor suppressor factor (SILK *et al.*, 2013; WEAVER *et al.*, 2007). Moreover, c-Myc induced genetic instability could be separated from its transforming activity at least at the level of DNA coding sequence (FEST *et al.*, 2005). Fest and associates investigated genomic instability triggered by either wild-type or deletion box II Delta106-Myc proteins. For this purpose, they used a mouse model of Burkitt's lymphoma spontaneously immortalized pro-B-lymphocytes (Ba/F3). Both tested versions of proteins mediated chromosomal rearrangements, while wild type but not Delta106-Myc expressing Ba/F3 cells triggered tumorigenesis in SCID mice upon transplantation. Therefore, authors concluded that genomic instability and tumorigenesis could be uncoupled.

c-Myc induced genomic instability is enhanced if p53 is downregulated or absent. In their study Mai and Wiener used the model of mouse plasmacytomas (PCTs) that is characterized by *c-Myc* activation upon translocations that juxtapose this oncogene onto one of the immunoglobulin loci (MAI and WIENER, 2002). The authors induced plasmacytomas in p53-deficient mice and revealed that absence of p53 tumor suppressor accelerates tumorigenesis but also causes change in the typical translocation patterns. Authors concluded that absence of p53 affects resistance, latency, and incidence of PCT development and influences translocation frequencies. Fukasawa et al. examined effects of the absence of p53 in vivo using the model of p53 -/- mice (FUKASAWA *et al.*, 1997). The authors detected a substantial elevation in the number of cells overexpressing c-Myc in these mice. Numerous p53-/- cells characterized by increased expression of c-Myc were also distinguished by amplification of genes as c-myc, dihydrofolate reductase (DHFR), and carbamoyl-phosphate synthetase-aspartate transcarbamoyl-dihydroorotase (CAD). Results of Fukasawa and associates further specified that a significant number of aberrant cells had been eliminated through p53-independent pathways since apoptosis was often registered in cells isolated from p53-/- mice. The cells that entered the process of apoptosis contained abnormally amplified centrosomes, displayed aneuploidy, high levels of c-Myc expression, as well as gene amplification.

c-Myc affects nuclear architecture

Not so long ago it was taught that identification of c-Myc target genes should finally define function of this gene and its role in genomic stability and tumorigenesis. At first, microarray technology gave us huge excitement when potential c-Myc target genes were

identified in several studies (MARINKOVIC *et al.*, 2004a; SCHULDINER and BENVENISTY, 2001). These studies produced never-ending stream of potential c-Myc targets and gave as confusingly complex view into thousands of genes and their interactions. Microarray studies and functional genomics approach led us to conclusion that c-Myc can control nuclear architecture in global fashion since about 15% of all cellular genes are regulated by this transcription factor (KNOEPFLER, 2007).

Whether *c-Myc* affects nuclear architecture and whether this remodeling has an impact on genomic stability was discussed in several scientific papers. Two independent research groups reported that c-Myc has the ability to structurally alter chromosomes through telomeric fusions, thus reordering the genetic information (LOUIS *et al.*, 2005; MAI and GARINI, 2005). They demonstrated that c-Myc overexpression induces telomeric aggregations in the interphase nucleus, thus leading to new breakage-bridge-fusions of the chromosomes and nonreciprocal translocations. Remodeling of the organization of telomeres leads the onset of genomic instability and afterward to chromosomal rearrangements. Moreover, it was found that c-Myc has role in Robertsonian (Rb) translocation chromosome creation in mouse cells by telomere fusions at centromeric termini of telocentric chromosomes (GUFFEI *et al.*, 2007). Obviously, c-Myc deregulation results in nuclear remodeling and positioning of telomeres and chromosomes. Chromosome remodeling enables chromosomal rearrangements through a combination of telomere dysfunction and chromosomal movements (KUZYK and MAI, 2014). Therefore, c-Myc affects nuclear organization and has direct role in remodeling of chromosomes, genes and their structural order. Nuclear remodeling is one of the prerequisites for cell transformation and tumorigenesis.

CONCLUSSIONS

There is an approximation that around 70% of all tumors are characterized with certain misregulation of c-Myc that affects its target genes regulation and amplification and overall organization of the nucleus. These changes are prerequisite for genomic rearrangements and subsequent process of tumorigenesis. Overall manifestation of c-Myc deregulation in many tumors and different mechanisms of Myc's action toward genomic stability suggest that this gene plays a central role in destabilization of genome.

Over the past few decades, a large number of data facts was accumulated confirming c-Myc's role in inducement of genomic instability and tumorigenesis. The differences in obtained data might be the consequences of the cell systems and animal models that were used for this purpose. The cell systems differs in the type of the cultured cell lines, expression constructs, type of the cell culture media and serum concentration, conditions of cell incubation etc. Besides, cells are cultivated in vitro in the presence of oxygen that induce production of ROS and DNA damage, and during cultivation genomic instabilities accumulate with each cell passage. Mouse strains mostly used as animal model vary in their susceptibility to process of tumorigenesis. Still there is an opened question how similar are these systems to natural conditions in which *c-Myc* is deregulated by several potential mechanisms. Nevertheless, the fact that many tumors maintain their malignant phenotype only when Myc protein deregulation persist, further potentiate that Myc-induced genetic alterations are crucial for process of tumorigenesis. We hope that further investigation on interactions between key mechanisms of c-Myc induced genomic instability will provide answer for solution of complex puzzle of Myc-directed carcinogenesis.

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DEREGULACIJA *c-Myc* GENA INICIRA KOMPLEKSAN PROCES GENOMSKE NESTABILNOSTI

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Izvod

Genetička stabilnost je ključna za integritet ćelije, a nemogućnost njenog održavanja dovodi do nagomilavanja grešaka usled procesa replikacije DNK, ćelijskog metabolizma, dejstva endogenih i egzogenih faktora koji oštećuju DNK, i konsekventno do inicijacije i napredovanja tumora. Široko prisutna deregulacija *c-Myc* gena u mnogim tumorima i različiti mehanizmi njegovog dejstva na genomsku stabilnost sugerišu centralnu ulogu ovog gena u destabilizaciji genoma. Studije izvedene primenom DNK mikročipova i pristupom funkcionalne genomike navele su nas na zaključak da c-Myc vrši globalnu kontrolu nuklearne arhitekture uzevši u obzir činjenicu da je oko 15% svih ćelijskih gena kontrolisano putem ovog transkripcionog faktora. Deregulacija *c-Myc* gena inicijalni je signal za složen process genomske nestabilnosti koji može da rezultira različitim ishodima kao što su: lokus-specifična amplifikacija, formacija ekstrahromozomalnih elemenata, hromoszomska nestabilnost, razmene delova nehomologih hromozoma, tačkaste mutacije, DNK prekidi i jedarska reorganizacija. Ovaj pregledni rad razmatra narastajuće dokaze da *c-Myc* onkogen inicira kompleksan process genomske nestabilnosti i diskutuje sisteme i uslove pod kojima promena regulacije ekspresije *c-Myc* gena ishoduje specifičnim tipovima genomskih promena.

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