c-MYC-Induced Genomic Instability

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MYC dysregulation initiates a dynamic process of genomic instability that is linked to tumor initiation. Early studies using MYC-carrying retroviruses showed that these viruses were potent transforming agents. Cell culture models followed that addressed the role of MYC in transformation. With the advent of MYC transgenic mice, it became obvious that MYC deregulation alone was sufficient to initiate B-cell neoplasia in mice. More than 70% of all tumors have some form of c-MYC gene dysregulation, which affects gene regulation, microRNA expression profiles, large genomic amplifications, and the overall organization of the nucleus. These changes set the stage for the dynamic genomic rearrangements that are associated with cellular transformation.

Genomic instability is an enabling feature of cancer cells (Hanahan and Weinberg 2011). MYC is one of its drivers and will be reviewed in this article from its early days to the present. Special focus will be given to MYC's ability to induce genomic instability and DNA damage at multiple levels, its ability to remodel the architecture of a cell's nucleus, and ultimately, its ability to promote neoplasia.

EARLY DAYS OF MYC

Tumor virology, which paved the way for the discovery of oncogenes, began in 1909 with F. Peyton Rous' isolation of the Rous sarcoma virus (Rous 1910, 1911). His "discovery of tumor-inducing viruses" was rewarded with the Nobel Prize in Physiology or Medicine in 1966. In 1989, the Nobel Prize was awarded to J. Michael Bishop and Harold E. Varmus for

their discovery of cellular oncogenes (*c-onc*). Specifically, they showed that the tumor viruses carried a gene derived from cellular DNA that when captured by the virus became an oncogene or cancer-causing gene (Stehelin et al. 1976).

Early studies of transforming viruses led to the discovery of the MYC oncogene. Avian leukosis virus-induced bursal lymphomas were first reported by Ellerman and Bang (1908). Subsequently, a series of avian retroviruses, including MH2, OK10, MH29, and CMII (Duesberg and Vogt 1979; Bister and Duesberg 1980), were isolated and found to contain MYC sequences (Chiswell et al. 1981; Bunte et al. 1983; Hann et al. 1983; Kan et al. 1983; Thompson et al. 1987). The name MYC originated from "myelocytomatosis," which consists of avian leukosis (hematopoietic neoplasm) and sarcomas. The viral MYC (*v-MYC*) transcript encodes a chimeric protein that usually includes

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a portion of the retroviral structural protein encoded by the GAG gene. During this same time period, Hayward et al. (1981), Neel et al. (1981), Cooper (1982), Payne et al. (1982), and Neiman et al. (1985) documented insertional activation of the *c-MYC* gene by the nononcogene-containing avian leukosis virus, which integrated into and activated the nearby *c-MYC* gene in bursal lymphomas (Payne et al. 1982).

Balanced chromosomal translocations of *MYC* in Burkitt's lymphoma documented it as a human oncogene (Manolov and Manolova 1972). Translocations are not only found in Burkitt's lymphoma (Zech et al. 1976), but also in mouse plasmacytoma (Ohno et al. 1979) and rat immunocytoma (Pear et al. 1986). The translocation of the *MYC* gene juxtaposes it to one of the immunoglobulin (IG) enhancers, which stimulate constitutive *MYC* expression, driving the neoplastic process (Dalla-Favera et al. 1982; Shen-Ong et al. 1982; Taub et al. 1982).

Transgenic mouse models further documented the causative role of *MYC* in tumorigenesis, with the first *MYC*-dependent mouse model of lymphoma created by Adams et al. (1985), allowing deeper insights into *MYC*-driven neoplasia (discussed in the following section).

TRANSFORMING ACTIVITY OF MYC

Early studies implicated *MYC* in cell proliferation (Palmieri et al. 1983), but it was insufficient for cellular transformation unless it cooperated with a second oncogene, *RAS*, to transform primary embryo fibroblasts (Land et al. 1983, 1986). In contrast, *MYC* alone was able to transform immortalized Rat1A fibroblasts (Eilers et al. 1989). Transformation was reversible and strictly dependent on *MYC* levels (Eilers et al. 1989). Similarly, Felsner and Bishop (1999a) observed reversible *MYC*-dependent tumorigenesis in the lymphoid lineage. Further investigations confirmed these early findings: *c-MYC* induced mammary tumorigenesis was shown to be reversible when *MYC* activation was experimentally terminated and *KRAS2* was not mutated. However, transformation was irreversible when *KRAS2* was mutated (D'Cruz et al. 2001), suggesting that genetic alterations subsequent

to *MYC* activation contribute to tumor progression. In this regard, it is notable that *MYC*-induced murine lymphomas regressed with *MYC* inactivation unless there were associated complex genomic alterations that allowed tumors to progress and become independent of *MYC* (Karlsson et al. 2003a,b).

MYC INDUCES GENOMIC INSTABILITY AND DNA DAMAGE

The studies that investigated *MYC*'s role in the promotion of genomic instability started with the notion that this nuclear oncogene was able to transform cells when deregulated (see previous section). *MYC* had been shown to enhance viral replication. However, a link to cellular replication, replication stress, and gene amplification was suspected, but not yet proven, when studies into *MYC*-mediated genomic instability were initiated.

MYC and DHFR

The first cellular gene investigated in association with *MYC* and genomic instability was the *dihydrofolate reductase* (*DHFR*) gene (Denis et al. 1991). The investigators found *DHFR* gene amplification and *MYC* protein elevation after methotrexate (MTX) drug selection. They observed that experimentally overexpressed *MYC* elevated *DHFR* copy number within 3 weeks. The investigators found that *MYC* up-regulated the numbers of MTX-resistant colonies containing 10-fold amplification of the *DHFR* gene. The enhanced amplification was induced by both *MYC* and MTX as well as when *MYC* was induced before the addition of MTX, albeit to a lower level (threefold). Although this work was highly relevant to the question of whether *MYC* promoted genomic instability of cellular genes, the combination of oncogene deregulation and MTX drug selection complicated the analysis.

Our first studies aimed to dissociate *MYC* gene deregulation from drug selection and possible clonal evolution that tends to occur in cells grown over several weeks (Lacoste et al. 2010). We focused on mouse, rat, hamster, and human

cells, in which a single transient conditional expression of c-MYC led to the locus-specific amplification of the *DHFR* gene (Mai 1994; Mai et al. 1996b). Our studies did not involve drug selection and did not allow the cells to propagate over a 3-week period. Instead, we observed *DHFR* copy number gains within 72 h after conditional MYC expression (Fig. 1).

We documented copy number increases of *DHFR* in the whole cell population by Southern blot analysis and also performed fluorescent in situ hybridization (FISH) to clarify whether there were individual cells or cell subpopulations that showed *DHFR* gene amplification when c-MYC was transiently overexpressed. Indeed, every cell expressing the conditional MYC gene showed *DHFR* amplification. Using a mouse mammary tumor virus long terminal repeat (MMTV-LTR)-driven c-MYC cDNA (exons II and III) and a single dexamethasone induction in independent stably transfected Chinese hamster ovary clones, we noted that *DHFR* gene amplification was a c-MYC-dependent genomic change in all cells examined (Mai 1994). This amplification was transient when c-MYC deregulation was induced only once (Fig. 1) (Mai et al. 1996b). During this process of transient and reversible *DHFR* gene amplification, other cellular genes that were studied remained single copy (Mai 1994; Mai et al. 1996b).

We next determined whether MYC-mediated *DHFR* gene amplification was dependent on the cell system used and found *DHFR* gene amplification in mouse, hamster, rat, and human cells. Different inducible MYC clones (MMTV-LTR or MYC-estrogen receptor fusion protein [MYCER- or MYCER]-driven conditional MYC expression) yielded the same results (Mai 1994; Mai et al. 1996b). Cells showing constitutive MYC deregulation (plasmacytoma cell line MOPC265, Colo320HSR, T47D) also displayed *DHFR* gene amplification and showed additional rearrangements of the locus (Mai et al. 1996b).

Finally, because all these data were derived from cell lines, we investigated MYC-associated *DHFR* gene amplification in vivo in the pristane-induced mouse plasmacytoma model (Taylor and Mai 1998). Indeed, the *DHFR* gene was amplified based on Southern blot and FISH analyses, and this amplification occurred in vivo subsequent to MYC deregulation within the first week of pristane-induced plasmacytoma genesis.

In human preinvasive cervical cancer, *DHFR* was also amplified in association with c-MYC overexpression (Gujion et al. 2007). The higher the level of MYC, the higher the numbers of cells exhibiting *DHFR* gene amplification (Gujion et al. 2007). A study by Arvanitis and Spandidos

Figure 1. MYC-dependent transient amplification of the *DHFR* locus. *DHFR* gene amplification is dependent on MYC overexpression. Partial metaphases showing a transient *DHFR* gene copy number increase before (left), during (middle), and after (right) a single conditional deregulation of MYC expression. *DHFR* is shown in green, the chromosomes in blue. (From Mai et al. 1996b; quantitative measurements of these signals have been reprinted, with permission.)

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(2008) next described the deregulation of the G₁/S transition in intraepithelial lesions and cancer of the cervix and found, among other alterations, MYC and *DHFR* elevation. Scionti et al. (2008) validated MYC levels and MTX resistance at diagnosis in osteosarcoma and found a direct correlation of MYC levels with MTX resistance. Down-regulation of MYC made the cells more sensitive to MTX. Studies in prostate cancer, prostate cancer cell lines, and metastasis-derived cell lines described a gain in 5q (El Gedaily et al. 2001; Lensch et al. 2002).

MYC-driven *DHFR* amplification occurred both intrachromosomally and extrachromosomally; increased *DHFR* copy numbers were seen within the chromosome with and without rearrangement of the locus and on extrachromosomal elements (Benner et al. 1991; Windle et al. 1991; Mai 1994; Mai et al. 1996b). Both genetic changes lead to additional copy numbers, but point to complex molecular remodeling by breakage, repair, and aberrant replication (see below).

MYC and Other Genes in Genomic Instability

c-MYC deregulation does not just affect *DHFR* gene copy numbers. Work over the years has illustrated a number of genes that are amplified as a result of c-MYC overexpression. These amplifications were all found within 72 h and as a result of a single experimentally induced deregulation of MYC. Chromosomal and extrachromosomal increases in their gene copy numbers were shown by Southern blotting, FISH, and by assessment of isolated extrachromosomal elements (EEs; see also MYC and Extrachromosomal Elements). The affected genes include *ribonucleotide reductase R2 (R2)* (Kuschak et al. 1999), the carbamyl-P synthetase, aspartate transcarbamylase, dihydro-orotase (CAD) enzyme-encoding gene (Miltenberger et al. 1995; Fukasawa et al. 1997; Chernova et al. 1998; Eberhardy and Farnham 2001), *ornithine decarboxylase* (George et al. 1996; Rounbehler et al. 2009), *cyclin B1*, and *cyclin D2* (Mai et al. 1999, 2005). The amplification of genes involved in DNA synthesis and cell-cycle progression will provide a proliferative advantage to cells that

harbor it (Kuschak et al. 2002). Not only will cells carrying such amplifications experience a growth advantage, but they will also be resistant to some of the cytotoxic drugs such as MTX (Denis et al. 1991) or even radiation (Lücke-Huhle et al. 1997). It is of note that permissivity to *DHFR* gene amplification correlates with metastatic potential (Lücke-Huhle 1994).

Certainly, this list only contains a few targets that were examined in this context, and there are many more as additional studies have shown. Rockwood et al. (2002) found that MYC deregulation was associated with illegitimate recombinations and long-range chromosomal rearrangements, but not point mutations. Illegitimate recombinations led to translocations, deletions, and inversions. DNA sequencing and spectral karyotyping indicated that many different chromosomal regions and breakpoints were involved (Rockwood et al. 2002). We now appreciate that c-MYC alters the stability of multiple genes and genomic sites, affecting noncoding RNAs and microRNAs (Huppi et al. 2008, 2011). Genome-wide approaches have helped map loci affected by MYC-driven instability in vivo. In bursal lymphomas, Neiman et al. (2006, 2008) showed that MYC deregulation was associated with tumor-specific palindrome formation that include inverted repeats and MYC binding sites. A consistently included palindrome was that of *bic/miR-155* that was associated with MYC-dependent bursal tumorigenesis and absent from control cells.

The list of genomic sites affected is large, with more than 11% of all cellular loci being candidates (Fernandez et al. 2003; Orian et al. 2003; Hulf et al. 2005). MYC/MAX heterodimers are estimated to occupy more than 15% of all gene promoters tested in Burkitt's lymphoma (Li et al. 2003), and more than 45% of all replication origins in human cells carrying MYC-binding E-box motifs (Swarnalatha et al. 2012). Candidate genes fall into diverse functional pathways such as cell-cycle-regulating genes, cell metabolism-associated genes, angiogenesis, cell adhesion, apoptosis, and metastasis (Grandori et al. 2000; Casillas et al. 2003; O'Connell et al. 2003; Meyer and Penn 2008; Dang 2012). Data by Levens' and Young's

groups indicate that MYC is a universal amplifier of gene expression in normal and tumor cells (Lin et al. 2012; Nie et al. 2012). Their data argue that MYC is not an on–off regulator of specific gene activity. Instead, MYC appears to regulate all active genes with the exception of immediate early genes in normal cells (Nie et al. 2012) and amplifies the expression of active genes in tumor cells (Lin et al. 2012; see also Levens 2013; Rahl and Young 2014). Distinct from this mechanism of enhanced gene expression and during the onset and propagation of genomic instability, MYC affects the genome through replication-driven, DNA damage- and stress-induced pathways. Moreover, MYC affects genome stability through the remodeling of nuclear architecture. These topics will be discussed in subsequent sections.

MYC and Extrachromosomal Elements

EEs are small circular DNA motifs that are not part of chromosomes. They are found in all organisms and as such are not associated with malignancy. EEs of normal cells carry mostly repetitive DNA motifs (Gaubatz 1990). They also occur as part of normal physiological processes, such as VDJ and T-cell receptor recombination (for review, see Kuttler and Mai 2007). EEs were noted again in recent work (Richards 2012; Shibata et al. 2012).

Tumor cells carry different types of EEs, the physiological type that is found in normal cells, but also larger EEs that contain genes. These are called episomes and double minutes, respectively, and are able to replicate; the latter will be distributed to daughter cells after cell division, albeit in unequal numbers.

c-MYC-induced EEs may be called episomes because they possess the ability to replicate (Smith et al. 2003). They carry MYC targets of locus-specific genomic instability and are transcriptionally competent or active and, therefore, functional genetic units (Smith et al. 2003). As expected from extrachromosomal genes that are able to be replicated and transcribed, the EEs carry histones, and thus behave as minichromosomes (Smith et al. 2003; for review, see Kuttler and Mai 2007). Importantly, EEs may be the sole

drivers of the neoplastic cell as seen in the extrachromosomal translocation of *MYC/IG* and MYC overexpression from these EEs in an otherwise chromosomal translocation-free mouse plasmacytoma (Wiener et al. 1999). Another example of extrachromosomal juxtaposition of genes is the *NUP214/ABL1* fusion in some cases of T-cell acute lymphoblastic leukemia that results in c-*ABL* deregulation (Graux et al. 2004). Whether MYC is involved in the latter fusion event is not known.

Karyotypic Instability

MYC not only alters single chromosomal loci, but promotes an overall induction of chromosomal instability, also termed karyotypic instability. Induced c-MYC deregulation results in a variety of chromosomal changes; among these are the formation of extrachromosomal elements (for review, see Kuttler and Mai 2007), centromere and telomere fusions (Mai et al. 1996a), chromosome and chromatid breaks, ring chromosomes, translocations, deletions and inversions, aneuploidy, and the formation of Robertsonian chromosomes (Fig. 2) (Mai et al. 1996a; Felsher and Bishop 1999b; Rockwood et al. 2002; Guffei et al. 2007; Gonçalves Dos Santos Silva et al. 2008; Silva et al. 2010; Chen et al. 2011). Recent reviews have addressed this role of MYC in instability (Dang et al. 2005; Prochownik and Li 2007; Prochownik 2008). Also, genome-wide approaches have highlighted MYC's overall potential to impact the genomic stability of the cell (Neiman et al. 2006, 2008). However, once instability is present, MYC does not always promote additional genomic instability (Gao et al. 2007).

p53, MYC, and Genomic Instability

MYC-dependent genomic instability is enhanced when *p53* is absent. The mouse plasmacytoma is an excellent model to address MYC-dependent instability in a *p53*-deficient background. Plasmacytomas (PCTs) are B-lineage tumors. In susceptible mice, PCTs are traditionally induced by mineral oils and plastic implants (Potter and Wiener 1992). These agents

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Figure 2. MYC-dependent karyotypic instability. (A) Shown are six individual and representative metaphase plates of Rat1A-MycER cells shown in the absence (a) and presence of transient MYC deregulation (b–f). Arrows highlight typical chromosomal aberrations, including chromatid breaks (b), centromere-telomere fusions (b–f) and the presence of ring chromosomes (f). Extrachromosomal elements are noted as well (f). (B) Centromeric staining reveals centromere–telomere fusions. Control Rat1A-MycER cells are shown in a. Centromere-telomere fusions are highlighted by arrows in b and c. Scale bars, 50 μm (A); 10 μm (B) (From Mai et al. 1996a; reprinted, with permission.)

cause chronic inflammation and allow the neoplastic development of PCTs that are all characterized by deregulated expression of MYC, which is caused by the chromosomal translocation of MYC to one of the immunoglobulin loci (Potter and Wiener 1992; Wiener et al. 1999).

Mouse strains susceptible to PCT development are BALB/c and NZB mice (Potter and Wiener 1992). Other mouse strains, such as

C57BL6 and 129Sv, are resistant to the classical induction schemes (Potter and Wiener 1992). To examine the impact of *p53* loss on PCT development, *p53*^{−/−} mice (Donehower et al. 1992) with a PCT-resistant genetic background of 75% C57BL6 and 25% 129Sv (Taconic Farms, Germantown, NY) were crossed with BALB/c congenics and examined in the presence or absence of one or two *p53* alleles (Mai and Wiener

2002). PCT development was then induced in these mice using pristane. The F1 ($p53^{+/-}$) mouse generation developed PCTs at a frequency of 11.5% (Mai and Wiener 2002). The number of pristane-induced PCTs increased to 42% in the N3 $p53^{-/-}$ mice of this mixed genetic background, but no PCTs developed in the respective N3 $p53^{+/+}$ controls. The mean latency in the N3 $p53^{-/-}$ mice was 146 days (range 97–316). The incidence was 37.5% with a mean latency of 189 days (range 126–266) in the $p53^{+/+}$ BALB/c controls (Mai and Wiener 2002). These data confirmed that the presence of $p53^{+/+}$ in the resistant background (C57BL6 and Sv129) inhibits PCT genesis, even in N3 mice. However, the absence of $p53$ overcomes the resistance to PCT development.

The next important finding of this study was the change in frequencies of common translocations observed in PCTs. The *c-MYC/IgH* translocation is the most common *MYC*-activating translocation in mouse PCTs (Potter and Wiener 1992). The ratio of the typical *c-MYC/IgH* translocation to the less frequent variant translocations, involving *MYG/Igκ* or *MYC/Igλ*, is 9 to 1. The *MYC*-activating translocations in $p53$ -deficient mice were both the typical and variant types with a 41.6% frequency for each (a 1:1 ratio). Translocation-negative tumors were also found in 16.6% of the cases. Extrachromosomal *MYC/Ig* translocation elements were frequently observed in these latter cases (Wiener et al. 1999; Mai and Wiener 2002). Thus the absence of $p53$ affected the resistance, latency, and incidence of PCT development and impacted on the most common translocation frequencies.

MYC and $p53$ are interconnected (Ragimov et al. 1993), such that deregulated *MYC* in $p53$ -deficient young mice induced genomic instability (Fukasawa et al. 1997). Not only was there a large number of cells expressing elevated levels of *c-MYC*, but the *MYC* target genes *DHFR* and *CAD* were also amplified both intrachromosomally and extrachromosomally. In addition, centrosome duplication was aberrant in vivo and aneuploidy was frequent. Remarkably, bone marrow, spleen, thymus, fibroblasts, and fetal liver cells displayed aneuploidy in the ab-

sence of $p53$ (Fukasawa 1996, 1997, 2007). The aneuploidy ranged from 5% in fetal liver cells to 34.8% in fibroblasts with 25.6% in thymocytes, 10% in bone marrow cells, and 20% in spleen cells from young (4- to 6-week-old) mice. *MYC*, *CAD*, and *DHFR* were coamplified in the same cells that showed *MYC* deregulation. Apoptosis was frequent in all organs examined, but less frequent in thymus.

c-MYC Mutants and Genomic Instability

Genomic instability of *MYC* can be separated genetically from its transforming activity. *MYC* mutants in *MYC box II* are defective in transformation of immortalized Rat1A cells (Eilers et al. 1989) and unable to induce tumors in vivo (Adams et al. 1985). Induction of instability by *MYC* mutant proteins was examined in Ba/F3 cells that conditionally expressed MycER-driven *MYC box II* mutants (B16 and $\Delta 106$) (Fest et al. 2002, 2005). These *MYC* mutants were able to induce, within 48 h, genomic instability that included structural and numerical aberrations, gene amplification, the formation of EEs, chromosomal breakage, increased aneuploidy, and polyploidization. However, telomeric aggregation was not induced and required a functional *MYC box II* (Caporali et al. 2007). In addition, instability associated with *MYC box II* deletion mutants was insufficient to promote tumorigenesis in mice (Fest et al. 2005). Thus, instability alone does not always enable neoplasia; it depends on the type and extent of instability. Too much instability prevents tumor development, probably by triggering apoptosis. This concept was clearly established by additional studies that focused on the level of tumor-promotion and tumor inhibition by aneuploidy in vivo (Weaver et al. 2006; Zasadil et al. 2013).

MYC and Replication versus Illegitimate Replication

Early data on *MYC* overexpression-mediated stimulation of replication of Simian Virus 40 (Classon et al. 1987, 1990; Henriksson et al. 1988) suggested that the oncoprotein played a role in DNA replication. This notion was heavily

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debated over the years; however, it turned out to be correct as postulated early on (Classon et al. 1987). Dominguez-Sola et al. (2007) showed that MYC was involved in normal DNA replication, specifically during the initiation of replication and during replication stress.

What happens when c-MYC is deregulated? How does it affect replication initiation? Studies by Li and Dang (1999), Gandarillas et al. (2000), and Pierce et al. (2004) gave the next insights into these questions. They showed that MYC deregulation could lead to DNA endoreduplication and polyploidy. In Li and Dang's work, MYC drove endoreduplication after a mitotic block. In Gandarillas' study, MYC up-regulation was followed by endoreduplication in keratinocytes before their terminal differentiation. Pierce et al. (2004) showed that Myc was required for larval endoreduplication in the absence of cell division (see also Gallant 2013).

Work by our group next showed that MYC was able to promote illegitimate DNA replication resulting in more than one replication firing per origin per cell cycle (Kuschak et al. 2002). Interestingly, in diploid synchronized PreB mouse lymphocytes, after a single pulse of conditional MYC deregulation, the *R2* gene was replicated more than once in early S phase (Kuschak et al. 2002). Using two-dimensional gel electrophoresis of DNA harvested before and throughout S phase as well as mitotic chromosomes from BrdU-pulse labeled cells, we found that MYC was able to deregulate the normal "once per cycle" replication initiation of *R2* that was observed in the control cells and for the control gene *cyclin C*. MYC forced three to four replication initiation forks and replication proceeded on both alleles, not just in a mono-allelic fashion as seen in control cells (Kuschak et al. 2002). MYC acted as an illegitimate replication-licensing factor. We concluded at this time that the types of *R2* amplification observed as a result of MYC deregulation were in agreement with replication-driven instability (Kuschak et al. 1999, 2002). Other genes that undergo MYC-dependent gene amplification, such as *Cyclin D2* and *DHFR*, also follow a replication-dependent mechanism (SF Louis and S Mai, unpubl.).

Recently, Swarnalatha et al. (2012) studied the epigenetic control of E-box binding and MYC-dependent replication initiation of *lamin B2*. The investigators documented cell-cycle-dependent epigenetic changes at the *lamin B2* E box and MYC occupancy as the cells entered S phase. MYC binding was followed by the recruitment of the minichromosome maintenance proteins and origin licensing. The investigators concluded that cross talk between histone modifications and MYC E-box binding is required for origin firing.

Barlow et al. (2013) recently identified MYC-induced DNA damage at early replication fragile and common fragile sites. Such replication stress-induced damage can result in chromosomal rearrangements. Hot spots of early replication fragile sites and common translocations frequently overlap in tumors (Barlow et al. 2013). This damage affects early fragile and common fragile sites in the whole genome. Thus, MYC affects more than single loci and effectively modifies the genome. The work on transcription and MYC by the groups of Levens and Young (Lin et al. 2012; Nie et al. 2012) promotes this concept on the transcriptional level. Dominguez-Sola et al. (2007) describe the global role for MYC in replication. Our data suggest that genes whose origins fire early in S phase are susceptible to MYC-dependent amplification (Kuschak et al. 2002; SF Louis and S Mai, unpubl.). For genomic instability to promote transformation and tumor progression, amplified and rearranged loci must provide a selective survival advantage and overcome the repressive effects of their microenvironment.

MYC and DNA Damage

MYC is not just a potent inducer of genomic changes as outlined. It has the ability to mediate DNA damage, as first described by Vafa et al. (2002). Vafa et al. (2002) provided evidence for DNA breaks caused by the reactive oxygen species (ROS) produced from brief MYC expression in normal human fibroblasts; this DNA damage occurred in the absence of apoptosis indicating that MYC overexpression may compromise the DNA damage response. The investigators sug-

gested that the increase in ROS may be the result of a biochemical imbalance caused by the sudden increase in gene products via MYC's transcriptional activation (Vafa et al. 2002).

The increased expression of MYC causes an accumulation of ROS, which generate DNA breaks (Khanna and Jackson 2001). ROS increase in both normal and serum-depleted cultures of NIH3T3 and Saos-2 MYC-overexpressing cell lines was described by Tanaka et al. (2002). More specifically, MYC induces a mitochondrial gene, *TFAM*, which encodes a protein essential for mitochondrial function and biogenesis, and may lead to increased ROS (Dang et al. 2005). *PRDX3*, which plays an important role in protection of ROS produced in hypoxic conditions, is also a target gene of MYC in Rat1a cells (Wonsey et al. 2002). Additional genes involved in ROS and regulated by MYC have been reviewed by Prochownik (2008). In in vivo studies, using a transgenic mouse model of hepatocarcinogenesis, overexpression of TGF- α and c-MYC led to chronic oxidative stress followed by impaired DNA damage response, genomic instability, and, ultimately, tumor progression (Hironaka et al. 2003).

However, a more recent study showed that MYC can also cause DNA double-stranded breaks (DSBs) independent of ROS production and proposed that DNA breaks may occur by different mechanisms based on the growth conditions (Ray et al. 2006). Using a MYCER-inducible system and immunofluorescence to stain for markers of single-stranded breaks (APE-1) and DSBs (γ -H2AX), the investigators found that on MYC induction, ROS-independent DSBs were observed in normal human foreskin fibroblasts cultured in normal (10%) serum in vitro and murine lymphocytes in vivo. In contrast, ROS-associated single-stranded breaks were observed for normal foreskin fibroblasts cultured in low (0.05%) serum and ambient oxygen saturation (Ray et al. 2006).

MYC and Replication Stress

MYC overexpression up-regulates transcription of numerous genes that consequently increase replication origin firing, a mechanism

that Campaner and Amati (2012) propose leads to an increase in the DNA damage accumulated during S phase. MYC can also override cell-cycle checkpoints that would otherwise dictate cell-cycle arrest. A brief increase in MYC activity accelerated Rat1A cells through the G₁/S transition and allowed these cells to continue to G₂ (Felscher and Bishop 1999b). This occurred even in the presence of *N*-(phosphonoacetyl)-L-aspartate, which normally arrests cells in S phase. MYC overexpression was found to uncouple DNA replication from mitosis as colcemid-arrested human and rodent cells continued to replicate their DNA resulting in apoptosis or polyploidy depending on p53 status (Li and Dang 1999). By comparing human foreskin fibroblasts to MYC-deficient rat cells, Robinson et al. (2009) observed that the deficient cells had a prolonged S phase, whereas the overexpression of MYC accelerated S phase; they also proposed a novel role for Werner DNA helicase (WRN) in S-phase acceleration (Robinson et al. 2009).

A third mechanism of replication stress involves disruptions in the repair of DSBs. The idea that MYC interferes with gene products that mediate DNA break repair was proposed by Karlsson et al. after their observation of severe magnitude increases in chromosome breaks in normal human foreskin fibroblasts through DSB assays (Karlsson et al. 2003). It was later determined by tandem affinity purification with mass spectral multidimensional protein identification technology proteomics that MYC regulates nonhomologous end-joining (NHEJ) factors (Koch et al. 2007), and a recent investigation concluded that MYC directly suppresses the NHEJ pathway causing inhibition of DSB repair and V(D)J recombination through inhibitory MYC *box II* binding with Ku70 in vitro and in vivo (Li et al. 2012). It has also been reported that MYC inhibits homologous recombination through regulation of RAD51 in various cancer cell lines (Luoto et al. 2010). Recently, Campaner and Amati (2012) have proposed that replication stress may result from metabolic starvation of nucleotides, or from a clash of RNA polymerase-mediated transcription and DNA replication machinery caus-

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ing replication fork collapse, mechanisms that both need experimental validation.

MYC AND DNA DAMAGE AND REPAIR

Although DNA damage can limit cellular lifespan, cells with overexpression of MYC also have an impaired DNA damage response and can activate DNA damage response (DDR) mechanisms that instead lead to genomic instability and tumor progression. MYC-induced DDR can act in both tumor-suppressive and tumor-promoting manners. The ataxia telangiectasia mutated (ATM) pathway is activated by DSBs and usually leads to apoptosis and halts malignant transformation. In contrast, the ataxia telangiectasia and Rad3-related (ATR) pathway allows for cellular proliferation and results in tumor progression. These competing pathways are reviewed by Campaner and Amati (2012).

Following DNA DSBs, the ATM protein kinase activates substrates involved in DDR, which ultimately leads to the activation of p53 and tumor suppression through apoptosis. Many studies have linked the ATM protein kinase to MYC; *ATM*^{-/-} mouse thymic lymphomas show extra copies of the chromosomal region harboring MYC (Liyanage et al. 2000), and B-cell tumors induced in *Eμ-MYC* transgenic mice have a reduced MYC-induced DDR and accelerated tumorigenesis with ATM loss (Adams et al. 1985). MYC overexpression was shown to induce the DDR through up-regulation of ATM. MYC overexpression was shown to activate ATM and p53 through phosphorylation and induce the DNA damage response as evidenced by the creation of γ-H2AX and phospho-SMC1 foci in vivo in a transgenic mouse model overexpressing MYC in squamous epithelial tissues (Pusapati et al. 2006). Furthermore, *Eμ-MYC; ATM*^{-/-} mice developed pre-B and B-cell lympho-leukemias that displayed shorter latency compared with *Eμ-MYC; ATM*^{+/+} and *ATM*^{-/-} mice that died of thymic lymphomas (Maclean et al. 2007). Also, in *Eμ-MYC*-induced mouse lymphomas, the loss of WIP1, which negatively regulates ATM, drastically delayed tumor onset (Shreeram et al. 2006). TIP60, which plays a role in the ATM DDR by inducing acetylation

of ATM in response to DNA damage (Sun et al. 2005), was proposed to be a haplo-insufficient tumor suppressor for pre- or early-stage lymphomas. *Eμ-MYC/Tip60*^{+/-} transgenic mice had accelerated tumors and an impaired DDR evidenced by decreased ATM phosphorylation compared with *Eμ-MYC/Tip60*^{+/+} mice (Gorrini et al. 2007). Tumors may evolve to develop mutations in this pathway to avoid tumor suppression; therefore, treatments that require a functional DDR will not be effective, but rather synthetic lethal approaches may be more successful (Bryant et al. 2005). For example, lymphoma cells from λ-Myc transgenic mice acquired inactivation of CHK2, which had a synergistic lethal interaction with the DNA repair inhibitor Poly (ADP-ribose) polymerase (Höglund et al. 2011b).

MYC regulates many DNA DSB repair genes such as *APEX*, *BRCA1*, *BRCA2*, *DNA-PKcs*, *Ku70*, *MSH2*, *NSB1*, *Rad50*, *Rad51*, and *Rad54L* (Menssen and Hermeking 2002; Chiang et al. 2003; Fernandez et al. 2003; Li et al. 2003; Luoto et al. 2010). MYC also regulates mismatch repair genes. For example, MYC down-regulation correlated with decreased levels of MSH2 and MLH1 in a gamma radiation-treated melanoma cell line (Bucci et al. 2005). It was also observed in hypoxic conditions in multiple tumor cell lines that the promoters of *MSH2* and *MLH1* changed from being occupied by MYC/MAX to MAX/MAD1 and MAX/MNT complexes (Bindra and Glazer 2007; see Hurlin 2013 and Conacci-Sorrell et al. 2014 for a description of the MXD/MNT proteins).

Overexpression of MYC also induces tumor-promoting DDR mechanisms. First of all, MYC was shown to up-regulate the WRN helicase, responsible for resolving unfavorable structures formed during S phase (Sidorova et al. 2008), through direct binding of its promoter by MYC/MAX complexes in four MYC-overexpressing cell lines (Grandori et al. 2003). In the absence of WRN, fibroblasts, non-small cell lung cancer cell lines, and *Eμ-MYC* transgenic mice with MYC activation showed an increase in the DDR and a delay in tumor growth (Robinson et al. 2009; Moser et al. 2012). Second, MYC plays a role in increasing nucleotide

synthesis to avoid nucleotide starvation from the increase in gene transcription. Liu et al. (2008) show this in multiple systems; chromatin immunoprecipitation with paired-end ditag sequencing analysis on a immortalized B-lymphocyte cell line, followed by qPCR on the products, showed that many genes involved in de novo nucleotide synthesis had E boxes in their promoters or first introns, were up-regulated on MYC induction, and therefore are candidates for being directly regulated by MYC. In MYC transgenic mouse livers, most of these target genes had increased expression on MYC induction. Also, when MYC was inhibited through lentivirus-based shRNAs in human metastatic melanoma cell lines, the genes encoding enzymes important for dNTP metabolism were repressed and the amount of dNTPs were reduced (Mannava et al. 2008). Last, Myc controls the ATR DNA repair pathway that is activated in response to specific single-stranded DNA produced during replication stress (Schoppy et al. 2012). Components of this pathway are also potential therapeutic targets as their inhibition in cells with Myc overexpression can result in increased DNA damage and trigger an apoptotic response. For example, inhibiting CHK1/CHK2 (proteins activated by ATR that in turn activate cell-cycle checkpoints, replication fork progression, and anti-apoptotic activity) (Cimprich and Cortez 2008; López-Contreras and Fernandez-Capetillo 2010) increases DNA damage, the DDR, apoptosis, and, ultimately, cell death in human cancer cell lines and in the *Eμ-MYC* mouse model of lymphoma (Cole et al. 2011; Ferrao et al. 2011; Höglund et al. 2011a,b). In a mouse model of Atr-Seckel syndrome, *Atr^{S/S} Eμ-MYC⁺* mice (hypomorphic for Atr) did not develop lymphomas, but *Eμ-MYC* aggravates Seckel syndrome symptoms (microcephaly, micrognathia, pancytopenia, and kyphosis) leading to their decreased survival time compared with *Atr^{+/+} Eμ-MYC⁺* mice (Murga et al. 2011).

In summary, the opposing tumor promoting and suppressive pathways enabled by MYC overexpression both provide potential opportunities for anticancer therapies. However, what remains to be resolved is how these pathways

interact in individual tumors and whether their competitive nature permits them to work in parallel, or if one pathway prevails. Only when this is clarified can the true value of therapeutic intervention be determined.

MYC and Nuclear Organization

c-MYC-induced genomic instability acts on the interphase nucleus, which it remodels such that dynamic processes of instability are initiated (for review, see Mai 2010; Gadji et al. 2011). Three-dimensional (3D) imaging has allowed us to investigate the impact of c-MYC on the organization of the nucleus (Chuang et al. 2004; Louis et al. 2005; Mai and Garini 2005, 2006; Vermolen et al. 2005). A single induction of deregulated c-MYC led to multiple changes in nuclear organization that altered the position and function of telomeres, selectively induced chromosome movement and overlap (Louis et al. 2005; Mai and Garini 2005), and induced Robertsonian fusions (Fig. 3A) (Guffei et al. 2007; Mai and Garini 2005). MYC deregulation for as short as 2–12 h resulted in nuclear remodeling of the 3D organization and position of telomeres and chromosomes (Louis et al. 2005; Mai and Garini 2005). Telomere remodeling led to the formation of telomeric aggregates and fusions that initiated breakage-bridge fusion cycles (Fig. 3B) (Louis et al. 2005; Mai and Garini 2005). Chromosome remodeling juxtaposed chromosomes that were usually found in distinct chromosomal territories and enabled chromosomal rearrangements. The latter appeared as a combination of telomere dysfunction and chromosomal movements (Louis et al. 2005; Mai and Garini 2005). These data sharpened our view on MYC-driven genomic instability and allowed us to understand that MYC affects nuclear organization and drives dynamic remodeling of chromosomes, genes, and their structural order. This is particularly relevant as gene activation, function, and nuclear space are functionally linked (Solovei et al. 2009). Nuclear remodeling occurs during early malignancy and sets the stage for neoplastic transformation (Mai and Garini 2005, 2006; Gadji et al. 2011, 2012).

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CONCLUDING REMARKS

Because of MYC's ability to induce cellular transformation through multiple pathways, the term "mutator phenotype" was coined for this oncoprotein (Beckman and Loeb 2005; reviewed in Prochownik 2008). MYC is deregulated in more than 70% of all cancers (Nesbit et al. 1999), and many of them are oncogene-addicted (Weinstein 2002); that is, they can only thrive and maintain their malignant phenotype when MYC protein deregulation persists (Felsner and Bishop 1999a; Jain et al. 2002; Gabay et al. 2014). Once new mutations are introduced,

MYC deregulation seems to be no longer required (D'Cruz et al. 2001) suggesting that additional genetic changes will then replace MYC and preserve the tumorigenic phenotype.

MYC overcomes replicative, oncogene-, and stress-induced senescence. By activating or repressing the genes involved in cellular proliferation, tumor suppression, DNA repair, apoptosis, angiogenesis, and invasion, although inducing a wide range of DNA damage and genomic instability, MYC acts as a master regulator of tumor development. In addition, it remodels the nuclear architecture of the cells in which its expression is deregulated and therefore affects the

Figure 3. MYC-dependent chromosomal rearrangements subsequent to nuclear chromosome and telomere remodeling. (*Legend continues on following page.*)

Figure 3. (A) Examples of fused and dicentric chromosomes that form as a result of c-MYC deregulation. (a) Spectral karyotyping (SKY) analysis. c-MYC-dependent formation of dicentric chromosomes (see arrows). *Left* panel: raw spectral image of a metaphase, *middle* panel: spectral image of the same metaphase, *right* panel: inverted DAPI image of the same metaphase, *bottom* panel: spectral karyotype of the above metaphase. (b) Additional examples of chromosomal fusions as determined by SKY. (B) Overview of c-MYC-dependent remodeling of the interphase nucleus. The figure illustrates the formation of telomeric aggregates that represent, in part, telomeric fusions and move chromosomes into closer vicinity to each other. In anaphase, dicentric chromosomes break generating unbalanced translocations and two telomere-free chromosomal ends. The latter will fuse with new chromosome partners, thus initiating breakage bridge-fusion (BBF) cycles. c-MYC deregulation induces multiple such BBF cycles. (From Mai and Garini 2005; images and legends reproduced with permission.)

positional organization of telomeres and chromosomes, which, in turn, initiate a dynamic process of ongoing genomic instability. The inhibition of MYC at early stages of tumor initiation should be a major goal of cancer therapy (see McKeown and Bradner 2014).

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