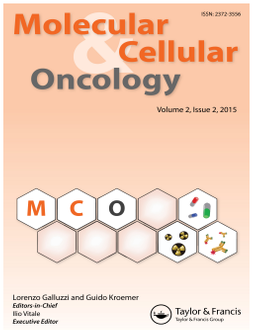

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AUTHOR'S VIEW

Cancer cells activate damage-tolerant and error-prone DNA synthesis

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ABSTRACT

Trans-lesion synthesis (TLS) is a DNA damage-tolerant and error-prone mode of DNA replication. Recent work shows that many cancer cells coopt an aberrantly expressed germ cell protein, melanoma antigen-A4 (MAGE-A4), to activate TLS. MAGE-A4–induced "pathological TLS" provides a potential mechanism through which neoplastic cells can tolerate intrinsic and therapeutic genotoxicity while acquiring mutability.

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Cancer-testes antigens (CTA); DNA damage; genome maintenance; melanoma antigen-A4 (MAGE-A4); mutagenesis; RAD18; trans-lesion synthesis (TLS)

Recent work suggests a new way in which some cancer cells may achieve DNA damage tolerance by hijacking an aberrantly expressed germ cell protein to activate trans-lesion synthesis (TLS). TLS is a post-replication repair mechanism that permits ongoing DNA synthesis in cells harboring damaged genomes, thereby sustaining cell proliferation and viability. When replication forks encounter bulky DNA lesions, conventional replicative DNA polymerases are transiently replaced with specialized DNA damage-tolerant "Y-family" DNA polymerases. Collectively, the Y-family TLS polymerases (POLH, POLK, POLI, and REV1) perform replicative bypass of diverse DNA lesions arising from environmental, intrinsic, and therapeutic sources.[1] In the absence of TLS, stalled replication forks collapse and generate lethal DNA double-strand breaks (DSBs). However, Y-family polymerases are inherently error prone (particularly when replicating undamaged templates or bypassing non-cognate DNA lesions) and must be used in a limited and tightly regulated manner to avoid mutagenesis.

Arguably, the best evidence that TLS can promote malignancy is provided by sunlight-sensitive and skin cancer-prone patients with xeroderma pigmentosum-variant (XPV). Individuals with XPV have congenital defects in POLH, the TLS polymerase responsible for error-free bypass of ultraviolet (UV) radiation-induced DNA lesions.[2] UV-exposed XPV cells are hypermutable due to compensatory and error-prone bypass of non-cognate DNA lesions by alternative TLS polymerases when POLH is absent or functionally inactive. Thus, replication of UV-damaged DNA by the "wrong" DNA polymerases likely generates the mutations that drive skin carcinogenesis in XPV. However, with the exception of XPV, TLS polymerases are not considered to be dysfunctional in cancer. TLS is usually regarded as a housekeeping genome maintenance process in all somatic cells. Whether altered TLS activity contributes more broadly to tumorigenesis or whether TLS affects mutational signatures of cancer cells has not been addressed.

A new report shows that the TLS pathway is reprogrammed in many cancer cells, and may therefore play a more active role in carcinogenesis than previously suspected. Gao and colleagues defined a cancer cell-specific mechanism that sustains DNA damage-tolerant trans-lesion synthesis by stabilizing an apical mediator of the TLS pathway, the E3 ubiquitin ligase RAD18.[3] RAD18 initiates TLS by mono-ubiquitinating proliferating cell nuclear antigen (PCNA), a DNA polymerase processivity factor, and promotes recruitment of Y-family DNA polymerases to sites of DNA damage-induced replication fork stalling.[4] Gao et al. identified the cancer/testes antigen (CTA) melanoma antigen-A4 (MAGE-A4) as a novel binding partner and stabilizer of RAD18 in lung carcinoma cells.

MAGE-A4 is one of approximately 150 known CTA proteins that are typically germline restricted and absent from normal somatic cells but aberrantly overexpressed in many different cancers.[5] Members of the melanoma antigen (MAGE) family of CTAs share considerable structural similarity (particularly in the conserved core Winged-Helix A and Winged-Helix B domains).[6] The MAGE proteins lack any known enzymatic activity and are therefore presumed to function as adaptors or mediators.

Although some CTAs have well-defined developmental roles in the testes the contribution of MAGE proteins to normal germ cell function is unknown. MAGE proteins have received attention because of their tumor-specific expression, primarily because they represent potential targets for cancer immune therapy. However, several recent studies provide strong evidence that MAGEs (and some other CTAs) have biochemical activities that endow cancer cells with tumorigenic traits. Notably, work by Potts and colleagues identified multiple MAGE

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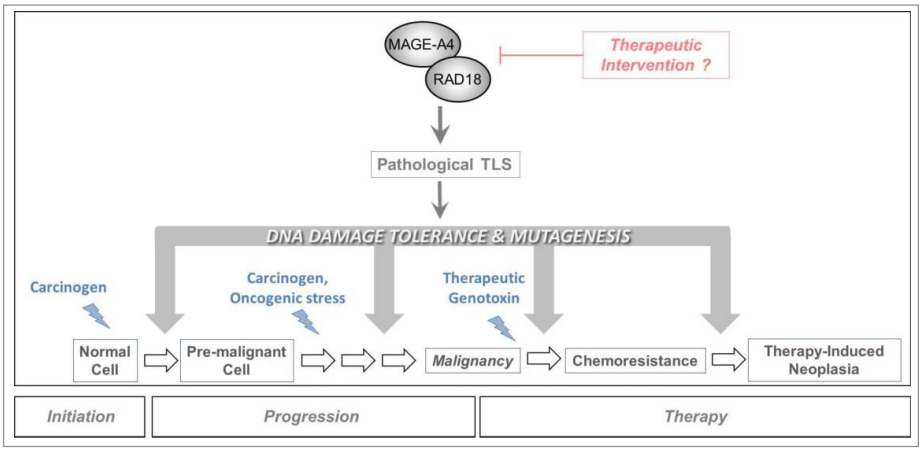

Figure 1. Potential roles of MAGE-A4–driven trans-lesion synthesis in tumorigenesis. Melanoma antigen-A4 (MAGE-A4)-induced TLS provides a mechanism by which neoplastic cells can tolerate carcinogenic exposures, oncogenic DNA replication stress, and therapy-induced DNA damage while promoting mutagenesis. The MAGE-A4–RAD18 signaling axis may provide opportunities for therapies that are highly specific for cancer cells.

family members as activating binding partners of specific E3 really interesting new gene (RING) ubiquitin ligases.[7] Those studies showed that the MAGE-C2–TRIM28 complex targets p53 (also known as TP53) for degradation, thereby attenuating important tumor-suppressive functions.[7] More recently, the Potts group reported that MAGE-A3/6–TRIM28 ubiquitinates and degrades AMPKα1 (or PRKAA1) and leads to inhibition of autophagy.[8] Given the emerging paradigm that MAGEs reprogram ubiquitin signaling networks in cancer cells, it is important to define the full repertoire of MAGE–E3 ligase complexes, identify their effector pathways, and test their roles in cancer. The recent work by Gao et al.[3] adds genome maintenance to the list of ubiquitin-mediated processes that are rewired by MAGEs in cancer cells. This study shows that several cancer cell lines rely on MAGE-A4 to maintain RAD18 levels, recruit POLH to UV-damaged chromatin, avert accumulation of double-strand breaks, and resume DNA synthesis following UV irradiation. MAGE-A4–depleted cells recapitulate many hallmarks of TLS deficiency, consistent with a MAGE-A4–RAD18 signaling axis that sustains TLS in neoplastic cells.

What then is the putative selective advantage or tumorigenic trait conferred by CTA-induced pathological TLS in cancer cells? Mutagenesis and DNA damage tolerance impact every aspect of carcinogenesis (Fig. 1). For initiation of carcinogenesis, cells must survive genotoxic stress, and permanently "fix" mutations via error-prone replication of damaged DNA. Preneoplastic and malignant cells often exist in harsh and stressful DNA-damaging environments. How neoplastic cells tolerate the inherent stresses of tumorigenesis (including oncogene-induced replication stress and reactive oxygen species) is not well understood. How DNA replication machinery is dysregulated to generate most of the mutations found in cancer genomes is also unknown. Cancer cells depend heavily on both DNA damage tolerance and mutagenesis to survive, adapt, and resist chemotherapy. Thus the high-capacity TLS conferred by MAGE-A4–RAD18 signaling could potentially facilitate tolerance of genotoxic and replicative stress. Additionally, excessive and error-prone TLS due to MAGE-A4–RAD18 signaling represents a potential mechanism for mutagenesis, a defining feature and hallmark of cancer.[9]

Clearly, further work is needed to determine how MAGE-A4–RAD18 signaling influences the process of tumorigenesis and affects the genomic landscape of cancer cells. Indeed, a direct demonstration that any CTA affects tumorigenesis is still lacking. *In vivo* experiments using defined mouse cancer models are clearly necessary to test whether CTAs can contribute to initiation, progression, chemoresistance, or maintenance of tumors.

Regardless of whether CTAs directly promote carcinogenesis, the many recent studies that identify CTA-induced signaling networks in established cancer cells[3,7,10] may suggest new opportunities for highly selective targeted therapies. In this regard the MAGE-A4–RAD18 signaling axis is a very appealing therapeutic target pathway as neoplastic cells depend heavily on DNA damage tolerance and mutagenesis to survive, adapt, and resist therapy. In addition to its well-documented role in TLS, RAD18 activates several additional genome maintenance mechanisms including the Fanconi anemia pathway and homologous recombination.[4] Therefore, MAGE-A4 has the potential to stimulate tolerance and repair of diverse DNA lesions (bulky adducts, DNA cross-links, DSBs) that are induced by anticancer agents. MAGE-A4–RAD18-mediated dependencies on DNA damage tolerance and mutagenesis are vulnerabilities that could eventually be exploited to sensitize cancer cells to intrinsic or therapy-induced replicative stresses.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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