Cell Host & Microbe
Review

What's the Damage? The Impact of Pathogens on Pathways that Maintain Host Genome Integrity

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Maintaining genome integrity and transmission of intact genomes is critical for cellular, organismal, and species survival. Cells can detect damaged DNA, activate checkpoints, and either enable DNA repair or trigger apoptosis to eliminate the damaged cell. Aberrations in these mechanisms lead to somatic mutations and genetic instability, which are hallmarks of cancer. Considering the long history of host-microbe coevolution, an impact of microbial infection on host genome integrity is not unexpected, and emerging links between microbial infections and oncogenesis further reinforce this idea. In this review, we compare strategies employed by viruses, bacteria, and parasites to alter, subvert, or otherwise manipulate host DNA damage and repair pathways. We highlight how microbes contribute to tumorigenesis by directly inducing DNA damage, inactivating checkpoint controls, or manipulating repair processes. We also discuss indirect effects resulting from inflammatory responses, changes in cellular metabolism, nuclear architecture, and epigenome integrity, and the associated evolutionary tradeoffs.

Introduction

Microbial infections mount hostile attacks on host signaling pathways and cellular integrity. Perhaps nothing is as challenging to host cells as pathogen attacks on the host genome and processes that protect genome integrity. It is inevitable that in some contexts pathogen-induced genomic damage contributes to tumorigenesis, and as such, 20% of all human cancers are causally related to pathogenic agents (de Martel et al., 2012; Zur Hausen, 2009). Pathogens employ a plethora of strategies to harness or inactivate the DNA damage response (DDR), a host mechanism that protects genome integrity, and circumvent barriers imposed by DNA damage checkpoints (reviewed by Guerra et al., 2011; Turnell and Grand, 2012; Weitzman et al., 2010).

In this review, we compare the strategies employed by viruses, bacteria, and parasites to affect the host's DNA damage and repair pathways. We highlight specific direct and indirect mechanisms involved as well as the genotoxic outcomes of these host-pathogen interactions (see Figure 1). The evolutionary tradeoffs resulting from the impact of host-microbe interactions on genome integrity are also discussed. Studies of viruses, bacteria, and parasites highlight the importance of host cellular pathways that maintain genome and epigenome integrity and provide insights into therapeutic approaches to pathogen-induced tumorigenesis.

Genome Integrity and Tumorigenesis

While it is generally accepted that most cancers are genetically unstable, the origins of this instability and the molecular mechanisms responsible for inducing tumorigenic mutations and rearrangements are numerous and unclear in several cases. The resolution and scale of genetic instability varies considerably, from subtle sequence changes involving base substitutions, deletions, or insertions of a few nucleotides to aneuploidy and gross alterations in chromosome structure (Lengauer et al., 1998). Picking apart the role of specific initiators and drivers critical for tumor initiation remains a nontrivial challenge. Microbial infection can influence cellular functions that represent classical hallmarks of cancer, including stimulating proliferative growth, evading growth suppression, and preventing apoptosis, as well as emerging hallmarks, such as altered cellular energetics and avoidance of immune destruction (Hanahan and Weinberg, 2011; see also review by Mesri et al., 2014 in this issue). Infectious agents can act as direct carcinogens or can indirectly contribute to tumorigenesis through induction of chronic inflammation, leading to either localized mutational changes and/or global chromosomal defects, which are features of the cancer genomic landscape.

DNA Damage and Repair

Repair pathways recognize and restore a range of DNA anomalies, including mismatches, abnormal bases, stalled replication forks, single-stranded DNA nicks, and double-stranded DNA breaks (DSBs) (Friedberg et al., 2006) (see Figure 2). The mismatch repair (MMR), base excision repair (BER), and nucleotide excision repair (NER) pathways respond to specific lesions in DNA residues. DSBs present a particularly dangerous lesion and are repaired by two principal pathways: the error-prone nonhomologous end-joining (NHEJ) pathway functions in all phases of the cell cycle, while the high-fidelity homologous recombination (HR) pathway requires a template for repair and utilizes available sister chromatids during the S and G2 phases

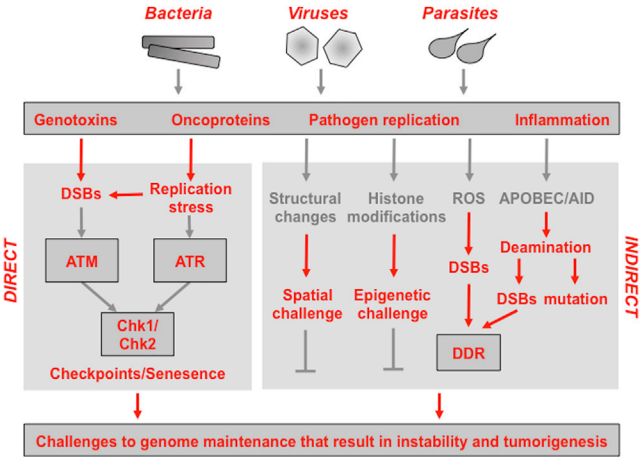

Figure 1. Interactions between Microbial Pathogens and Pathways that Maintain Host Genome Integrity

The schematic illustrates how infectious agents (viruses, prokaryotic bacteria, or eukaryotic parasites) associated with tumorigenesis converge on common strategies that challenge DNA integrity and genome stability. These include direct effects of pathogen-encoded genotoxins and oncoproteins as well as indirect outcomes of microbial infection and inflammatory responses. Please see the main text for detailed explanations of the host pathways that are impacted by the direct and indirect activities of microbial pathogens.

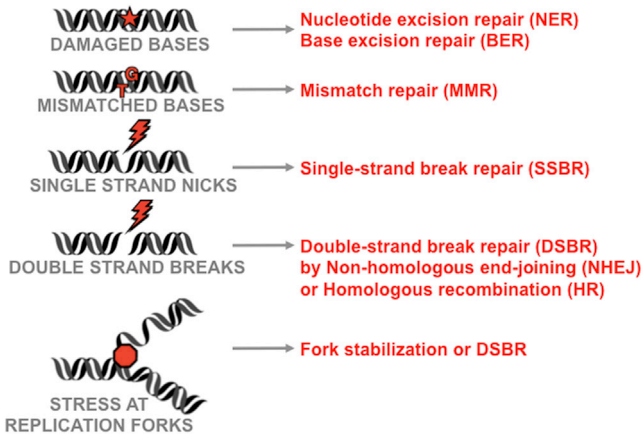

Figure 2. Common DNA Damage Intermediates and Repair Pathways

Although much of this review is focused on double-strand break repair pathways, many of these other repair processes can be impacted by microbial infections.

of the cell cycle (see Figure 2). In all cases, sensor proteins recognize the damage and activate signaling cascades to recruit mediators for repair and induction of proliferation checkpoints (reviewed by Ciccia and Elledge, 2010). DNA damage activates protein kinases, including the ataxia telangiectasia mutated protein kinase (ATM), the ATM and Rad3-related kinase (ATR), the DNA-dependent protein kinase (DNA-PK), and the downstream checkpoint effector kinases Chk1 and Chk2 (Ciccia and Elledge, 2010) (see Figure 3). In addition to phosphorylation, other posttranslational modifications (PTMs) are critical for the cellular DNA damage and repair machinery (reviewed by Polo and Jackson, 2011). Covalent, but reversible, modification by ubiquitin and SUMO recently emerged as crucial components of the cellular DDR (Jackson and Durocher, 2013). The DDR network is established through recognition of these PTMs by high-affinity binding modules, such as BRCT and FHA domains that bind phosphorylated epitopes (reviewed by Reinhardt and Yaffe, 2013), Tudor domains that bind methylated sites, ubiquitin-binding domains (UBDs), and SUMO-interacting motifs (SIMs) (Polo and Jackson, 2011). PTMs affect localization, protein-protein interactions, and protein activity to regulate damage recognition and repair processes.

Temporal regulation of damage recognition and repair is crucial to maintain genome integrity, and PTMs serve to recruit repair factors to damage sites. The ATM kinase is activated by DSBs, whereas ATR responds to single-strand DNA (ssDNA) resulting from resected DNA at breaks or stalled replication forks (Maréchal and Zou, 2013). Each DNA damage lesion has a specific damage sensor. Specifically, the Mre11/Rad50/Nbs1 (MRN) complex senses DSBs, whereas ATR is recruited to ssDNA bound by RPA through its cofactor ATRIP and is activated by binding proteins such as TOPBP1 (see Figure 3). Phosphorylation of the histone variant H2AX at DSB sites forms γH2AX, a marker of breaks. Phosphorylated γH2AX is bound by the mediator of checkpoints, MDC1, which is itself phosphorylated and then recognized by the FHA domain of the E3 ligase RNF8. Protein ubiquitination at DSBs signals the recruitment of RNF168, an E3 ligase with ubiquitin-binding domains. RNF8/RNF168-dependent ubiquitination promotes recruitment and retention of repair factors, and deubiquitinating proteins dynamically regulate ubiquitin chains at damage sites. Numerous DNA repair factors are SUMOylated in the DDR, and recognition by SIM binding promotes interactions at repair sites or can lead to turnover by SUMO-targeted ubiquitin ligases (Polo and Jackson, 2011). Acetylation also plays an important role in DSB repair, and the acetylase Tip60 is recruited to modify histones and DDR proteins (Price and D'Andrea, 2013). All these critical orchestrating events for the DDR can be perturbed by microbial infections, with detrimental consequences for host genomic integrity.

Pathogen Contributions to Tumorigenesis

It is recognized that infection is a major contributor to cancer, with certain infectious agents classified as direct human carcinogens (de Martel et al., 2012). Some pathogens encode proteins required to maintain their own genetic integrity (e.g., bacteria), whereas others rely extensively on the host machinery (e.g., viruses). Pathogens impact host cell genomes directly through genotoxins and oncoproteins that induce changes to cellular DNA and by impairing DNA repair mechanisms (see Figure 1). Genomic integrity is also impacted indirectly as a result of pathogen replication and induced inflammation. Microbial pathogens manipulate cellular environments to create conditions conducive to their own replication; they alter cellular structures, divert signaling pathways, modify host epigenetic programs, and influence metabolism. The host DDR cascades activated by pathogens serve to combat infection and can therefore be viewed as a branch of cellular defense. These are counteracted by numerous microbial strategies, with devastating consequences for host cells and the infected organism. Mining host and pathogen genomes provides insights into the intricate mechanisms that contribute to this dynamic interface and coevolution of defense and counterattack strategies in tumorigenesis.