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Review

Manipulation of cellular DNA damage repair machinery facilitates propagation of human papillomaviruses

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ABSTRACT

In general, the interplay among viruses and DNA damage repair (DDR) pathways can be divided based on whether the interaction promotes or inhibits the viral lifecycle. The propagation of human papillomaviruses is both promoted and inhibited by DDR proteins. As a result, HPV proteins both activate repair pathways, such as the ATM and ATR pathways, and inhibit other pathways, most notably the p53 signaling pathway. Indeed, the role of HPV proteins, with regard to the DDR pathways, can be divided into two broad categories. The first set of viral proteins, HPV E1 and E2 activate a DNA damage response and recruit repair proteins to viral replication centers, where these proteins are likely usurped to replicate the viral genome. Because the activation of the DDR response typically elicits a cell cycle arrest that would impeded the viral lifecycle, the second set of HPV proteins, HPV E6 and E7, prevents the DDR response from pausing cell cycle progression or inducing apoptosis. This review provides a detailed account of the interactions among HPV proteins and DDR proteins that facilitate HPV propagation.

1. Viruses and DNA damage repair

Because cellular DNA is constantly bombarded by exposure to endogenous and exogenous mutagens; a vast network of proteins, collectively referred to as DNA Damage Repair (DDR) machinery, has evolved in response to these insults. DDR pathways are capable of sensing damaged DNA, inducing a signaling cascade, and ultimately recruiting the DDR-specific nucleases, helicases, ligases, and polymerases necessary to pause cell cycle progression and repair the resulting lesions. Impressively, DDR pathways repair an estimated 10,000 lesions per cell per day [1].

Although there is some interplay between the pathways, specific repair pathways are generally dedicated to the repair of particular types of damaged DNA. As an overview, Fig. 1 depicts three common forms of damaged DNA and some of the proteins/pathways that are activated in response to these lesions. For example, while the PI3 kinase ATM is activated by phosphorylation in response to double strand breaks in DNA (DSBs), a related PI3 kinase ATR and its interacting partner ATRIP respond to intrastrand crosslinks in DNA (Fig. 1). The activation of these kinases results in the initiation of downstream repair pathways. Similarly, in response to single strand breaks in DNA (SSBs), PARP1 and the MRN complex initiate repair of the lesion. Together, DNA repair pathways maintain the fidelity of the human genome (Fig. 2).

The importance of DDR proteins is not limited to protecting genomic material from these numerous insults. Indeed, many DDR proteins also play a role in the body's immune response. A subset of DDR proteins participate in the recombination of antibody genes that results in our almost unlimited diversity of antibody response [2]. Additionally, many of these same proteins play a role both in the cellular response to viral infections as well as the lifecycle of multiple viruses. In general, the interplay among viruses and DDR proteins can be divided based on whether the interaction inhibits or promotes viral propagation. In some cases, such as Adenovirus infections, host DDR pathways act to restrict viral propagation [3–5]. Predictably, many viruses that are adversely affected by host DDR machinery have evolved means to subvert the DDR response [6–14]. On the opposite end of the spectrum, other viruses, such as members of the herpesvirus, polyomavirus and papillomavirus families, rely on the host DDR response to replicate their genomes. This viral strategy involves the activation of DDR proteins and their recruitment to viral replication centers, providing viral replication centers access to DDR-associated polymerases that are independent of origin licensing requirements [15–27].

While many viruses exclusively employ one or the other of these two strategies, some viruses like the human papillomaviruses (HPVs) have more complicated relationship with host DDR pathways. HPVs both inhibit and activate different aspects of these pathways. What may seem like a paradoxical strategy is believed to allow the virus access to DDR proteins that facilitate replication of the viral genome while avoiding the cell cycle arrest that typically accompanies DDR activation. In this review, the relationship

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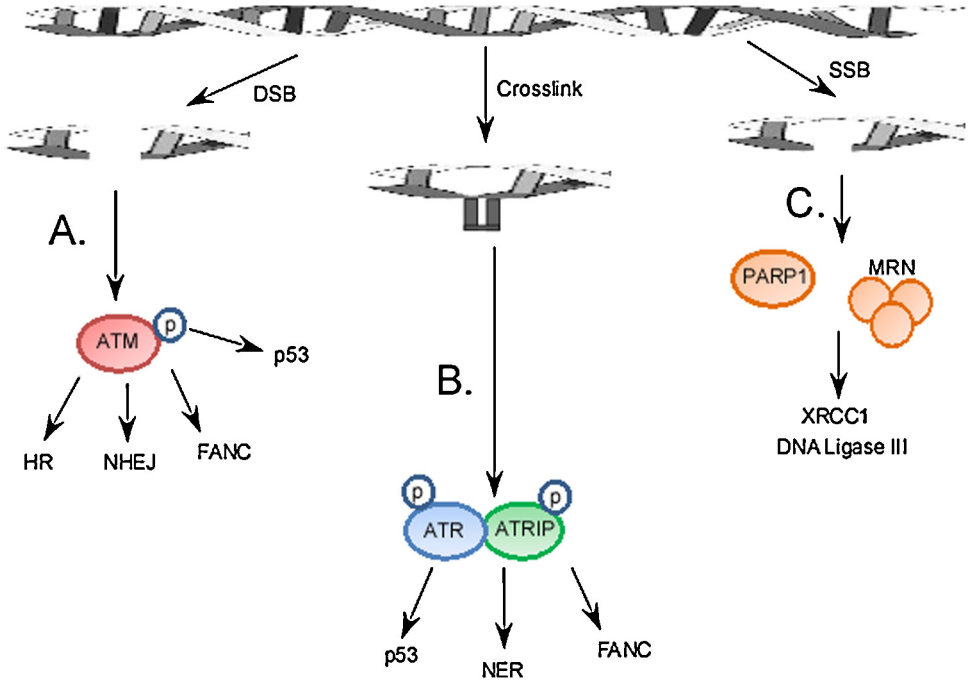

Fig. 1. Brief overview of DNA damage repair: three common types of DNA damage are depicted in this image as well as an summary of the pathways/proteins that are activated in response to each type of damage. (A) A double strand break DNA break (DSB) most often results in the activation, by phosphorylation (indicated in this figure by a circled p), of the PI3 kinase ATM. Multiple pathways are downstream of ATM including homology dependent DSB repair (HR), non-homologous end joining (NHEJ), the Fanconi Anemia pathway (FANC), as well as the p53 signaling pathway. (B) In response to intrastrand crosslinks (crosslink), ATR and its interacting partner ATRIP become activated and phosphorylated leading to the induction of several downstream pathways. The activated ATR/ATRIP complex induces the Fanconi Anemia repair and Nucleotide Excision Repair (NER) pathways, as well as the p53 signaling pathway. (C) Finally, a single strand DNA break (SSB) causes the activation of both PARP1 and the MRN (MRE11, RAD50, NBS1) complex and ultimately together with XRCC1, DNA Ligase III as well as multiple other repair proteins fixes the lesion.

between HPV propagation and host cell DNA damage repair will be explored.

2. Brief introduction on human papillomavirus

Human papillomaviruses (HPVs) are a large family of double strand DNA viruses that infect the mucus membranes and epidermis of humans. Although there are approximately 200 different types of HPVs divided among 5 genera, the most clinically relevant HPVs belong to the alpha-papilloma genus. As a result, most of the research on HPV proteins focuses on members of this genus; particularly those HPVs most closely connected with anogenital track cancers. Consequently, this review will focus primarily on interactions among cancer-associated alpha-papillomaviral proteins and cellular DDR proteins. However, although this review will concentrate on these particular HPVs, we will also highlight some key observations about other members of this family that help illustrate the common need for disrupting certain DDR responses.

3. Human papillomavirus and the DNA damage response

DDR is both inhibitory and necessary for the replication of HPVs and as a result HPV proteins both activate and inhibit DDR responses. Similar to the examples discussed above, HPV proteins, particularly HPV E1 and E2, stimulate DDR at sites of viral replication, most likely in order to allow the replication centers access to cellular replication machinery [28,29]. In response to damaged DNA, cell cycle progression is halted to allow time for repair of the damage to take place prior to attempting synthesis of new DNA from a faulty template. Because HPV replication can only occur in actively cycling cells, the viral E7 protein has evolved to push cells into a proliferative state despite contradictory signals, such as those elicited by HPV E1 and E2 induced activation of the DDR response. The ability of HPV E7 to drive cells through the cell cycle can have detrimental consequences, namely large scale genomic instability and damage. These insults to a cell's genomic material would normally lead to apoptosis. HPV E6, however, increases cellular tolerance of DNA damage by decoupling DDR signaling from apoptotic signaling. HPV E6, also, promotes continued advancement the cell cycle by directly inhibiting multiple DDR pathways. This review will discuss the stimulation and restriction of DDR response by HPV proteins in further detail (For a more general discussion of DDR and viruses see Lilley et al., 2007 [30])

4. A brief overview of the HPV lifecycle

The HPV lifecycle is tied to epithelial differentiation and can be divided into two phases, genome maintenance and genome amplification, based on markedly different replication strategies. Because the demands of these proliferative tactics differ widely, the interactions among viral proteins and cellular DDR proteins also vary greatly. To frame the later discussions, we will first briefly outline the replicative lifecycle of HPV, specifically highlighting the roles of viral and cellular DDR proteins. For a more thorough review of the HPV viral life cycle see Doorbar 2005 [31].

4.1. HPV genome maintenance

In the genome maintenance portion of the lifecycle, the viral episome is sustained at a steady copy number in the basal epithelium and viral replication is linked to cell cycle progression [31]. Viral genome maintenance requires both cellular replication machinery and at least the viral E1 and E2 proteins (some viruses also require HPV E7). While the role of DDR proteins in viral replication has not been completely elucidated, expression of HPV E1 activates the cellular DDR response and most of proteins activated in this response

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