The transformation of normal cells is often associated with mutations in genes that regulate cell proliferation and differentiation. Deregulated cell proliferation as a result of oncogene activation is an early hallmark of tumorigenesis and is thought to induce “replication stress,” causing DNA replication forks to progress slowly or stall. The factors that promote replication stress are not well understood, but may include the depletion of nucleotides and other molecules that are required for DNA synthesis, a deregulated firing of DNA replication origins, as well as the accumulation of DNA lesions that block replication forks, in particular in genomic regions that are intrinsically difficult to replicate. Oncogene-induced replication stress and the consequent collapse of replication forks result in DNA damage and the activation of the DNA damage response (DDR), a conserved signaling pathway that preserves genome integrity. Two key DNA damage sensor kinases of the DDR are ataxia telangiectasia and Rad3 related (ATR), and the ataxia telangiectasia, mutated (ATM), which are preferentially activated by single-stranded and double-stranded DNA breaks, respectively. In turn, ATR and ATM activate many downstream mediators including the Ser/Thr kinases CHK1 and CHK2, which phosphorylate effector proteins such as BRCA1, CCD25 and p53 family members that inhibit cell cycle progression and activate DNA repair systems or apoptosis, if the DNA damage cannot be repaired.

RAS

RAS is a membrane-associated GTP-binding protein that is activated by many growth factors and regulates various cellular functions, including proliferation, apoptosis and migration. In multiple human cancer, the activity of RAS is deregulated as a result of mutations that lock RAS in an perpetual “on state,” resulting in the activation of a number of signaling pathways, including the RAF-MAPK/MEK and the PI3K pathway. Oncogenic RAS initially drives a quick proliferation phase, which is followed by cell cycle arrest (senescence) due to replication stress and the activation of the DDR.

NKG2D

The DDR and other pathways activated in response to malignant transformation have been shown to upregulate ligands for the activating immune receptor NKG2D. NKG2D is expressed by all natural killer (NK) cells in humans, activated CD8+ T cells in mice and subsets of both γδ and NK T cells. Multiple NKG2D ligands have been identified in humans and mice, all of which are distantly related to MHC Class I molecules. Human NKG2D ligands include MICA, MICB and 6 different UL-16 binding proteins (ULBPs), otherwise known as RAET1 proteins. In mice, NKG2D ligands include 5 different isoforms of RAE-1 proteins, MULT1 and 3 different isoforms of H60 proteins.

Posttranscriptional Regulation of NKG2D Ligand Expression by RAS

We have recently demonstrated that the expression of NKG2D ligands is intimately linked to RAS activation. Overexpression of the RAS isoform H-RASV12 resulted in the upregulation of NKG2D ligands in mouse and human cell lines, and rendered tumor cells more susceptible to NK cell-mediated lysis. This effect depends on MAPK and PI3K signaling, but not on the DNA damage response.
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and may provide a barrier against tumorigenesis. In summary, NKG2D ligands expression may be a consequence of the activation of several oncogenic signaling pathways, including those involving RAS. NKG2D ligands may therefore constitute useful markers for detecting or targeting tumor cells that bear RAS activating mutations.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646-74; PMID:21376230; http://dx.doi.org/10.1016/j.cell.2011.02.013.
2. Burhans WC, Weinberger M. DNA replication stress, genome instability and aging. Nucleic Acids Res 2007; 35:7545-56; PMID:18055408; http://dx.doi.org/10.1093/nar/gkm1059.
3. Barikova J, Horejcí Z, Kood K, Krámer A, Tort F, Zieger K, et al. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 2005; 434:864-70; PMID:15829956; http://dx.doi.org/10.1038/nature03482.
4. Sancar A, Lindsey-Boltz LA, Umasal-Kaçmaz K, Linn S. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annu Rev Biochem 2004; 73:39-85; PMID:15189136; http://dx.doi.org/10.1146/annurev.biochem.73.011303.073723.
5. Karnoub AE, Weinberg RA. Ras oncogenes: split personalities. Nat Rev Mol Cell Biol 2008; 9:517-31; PMID:18568040; http://dx.doi.org/10.1038/nrm2438.
6. Di Micco R, Fumagalli M, Cicelese A, Piccinin S, Gasparini P, Luise C, et al. Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication. Nature 2006; 444:638-42; PMID:17136094; http://dx.doi.org/10.1038/nature05327.
7. Gasser S, Orolic S, Brown EJ, Raulet DH. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. Nature 2005; 436:1186-90; PMID:15995699; http://dx.doi.org/10.1038/nature03884.

8. Raulet DH. Roles of the NKG2D immunoreceptor and its ligands. Nat Rev Immunol 2003; 3:781-90; PMID:14523385; http://dx.doi.org/10.1038/nri1199.

9. Liu XV, Ho SS, Tan JJ, Kamran N, Gasser S. Ras activation induces expression of Rae1 family NK receptor ligands. J Immunol 2012; 189:1826-34; PMID:22798674; http://dx.doi.org/10.4049/jimmunol.1200965.

10. Jung H HB, Procyr E, Raulet DH. E2F Transcription Factors Regulate Expression of RAe1 Ligands for NKG2D, an Immune Cell Receptor Implicated in Tumor Surveillance. Submitted.