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NEK1 Protein Kinase as a Target for Anticancer Therapeutics

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Genomic instability is a hallmark of cancer and less frequently observed in non-cancerous cells. To maintain the stability of the genome, cells must safeguard the DNA passed on to daughter cells. Any DNA damages generated by exogenous or endogenous agents must be recognized through an efficient detection mechanism of the DNA lesions, and repaired with precision prior to cell division. DNA damages generate signals that normally arrest cell cycle progression until the damaged DNA is repaired. The DNA damage-repair signaling pathway is modulated by a group of precisely choreographed protein kinases [1]. This network activates a series of checkpoints that temporarily halt progression of the cell cycle and prevent the cell from duplicating its DNA or from undergoing mitosis until DNA can be assessed and repaired. For prompt and accurate DNA repair, signals must be conveyed rapidly and precisely. The ATM (ataxia-telangiectasia mutated) and ATR (ATM and Rad3-related kinase) kinases are the best examples of these protein kinases. ATR appears to be even more fundamental in DNA damage sensing and repair than ATM, since homozygous mutations of *ATR* have not been found in humans and since biallelic *Atr* inactivation in mice is lethal [2]. ATR and ATM have similar intersecting downstream targets and both are important for signaling and repairing of double strand breaks. ATR is thought to be the more important upstream PI3K for signaling and repairing UV radiation- and nucleoside analog-induced DNA damage, both of which cause stalled replication forks. Until recently, ATM and/or ATR were believed to be the crucial, proximal signaling molecules in all forms of DNA damage sensing and repair.

More recently, NEK1, the first cloned mammalian NIMA related protein kinase, was shown to have similarly important but distinct roles in DNA damage responses [3-6]. Like ATM- and ATR- deficient cells, NEK1-deficient cells were much more sensitive to the effects of ionizing radiation (IR)-induced DNA damage than otherwise identical wild type cells [5]. Cells with an inactivating mutation of murine *Nek1*, as well as in cells with NEK1 expression is silenced by RNA interference, don't repair damaged DNA as efficiently as control cells. NEK1-deficient cells have defective G1/S and M-phase checkpoints. NEK1 seems to oversee DNA damage responses in some ways like ATM and ATR, but it is unique and independent of both of these canonical kinases [6]. Failure of proper checkpoint responses has serious consequences: NEK1-deficient cells fail to repair damaged DNA after relatively low dose DNA damage. The damaged DNA in turn leads to defective chromatid pairing, chromosome breaks, mitotic missegregation, programmed cell death if the mitotic defects are severe, and to ultimately chromosome instability in subsequent generations of the surviving daughter cells. Several syndromes associated with defective DNA damage proteins ultimately result in Chromosome Instability [CIN], whether the defective proteins are involved directly in centrosome or kinetochore functions during mitosis or whether they instead function indirectly in maintaining orderly cell cycle checkpoints [7]. Like ATM and ATR mutant mice, mice heterozygous of NEK1 suffer from CIN phenotype and increased cancer incidences.

In addition to the role in DNA damage/repair pathway, NEK1 also regulates apoptosis pathway through interacting with mitochondrial outer membrane protein, VDAC1. Intrinsic cell death occurs when cytotoxic and genotoxic stresses cause irreparable mitochondrial and DNA damage. This form of cell death will remove the damaged cells before passing genetic mutations on to subsequent generations of cells, often without triggering an inflammatory response in neighboring cells. This form of intrinsic cell death is distinct from strictly defined apoptosis, i.e., the type that occurs during development [8]. In oxidative injury- and DNA damage- induced cell death, collapse of mitochondrial membrane potential (MPM) through opening of the mitochondrial permeability transition pore (MPTP) and subsequent mitochondrial permeabilization are seminal events. With loss the MPM, cyctochrome C is released from mitochondria into cytosol and activates the caspase cascade to initiate apoptosis. MPTP composes of VDAC1, the inner mitochondrial membrane protein ANT (adenine nucleotide translocator), and the inner mitochondrial membrane protein cyclophilin D (cypD) [9]. Through interaction and phosphorylation of VDAC1, NEK1 regulates the cytochrome C releases from mitochondria in the initiation step of apoptosis. In the basal state of a cell, NEK1 phosphorylates VDAC1, and seems to keep the mitochondrial transition pore intact. Without functional NEK1, cells lose the VDAC1 S193 phosphorylation when injured, as by a DNA damaging agent, and die even with a DNA damage dose that would not kill identical cells that express normal amounts of functional NEK1 [10,11]. Subsets of these cells that survive faulty DNA damage repair ultimately become polyploid, and are transformed into neoplastic cells.

Many kinase inhibitors have been developed to act alone or in combination with traditional chemotherapeutics [12,13]. The role of NEK1 in DNA damage response/repair pathway and apoptosis identifies NEK1 as a critical factor in determining the effectiveness of chemotherapeutics. Further, cells without functional NEK1 are hypersensitive to DNA damage from ionizing radiation and many other genotoxic agents. This phenotype makes NEK1 a great candidate for a rational drug design to abolish NEK1 functions and to treat cancer. In conclusion, a thorough understanding of the NEK1 pathway has revealed important roles Nek1 play in cellular response to chemotherapeutics.

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