SY-III-3 KILLING DOMAINS IN HNOXA "BH3 AND MTD" : WHO SHOULD BE BLAMED?

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hNoxa, a member of the "BH3-only" Bcl-2 family, has been originally identified as a transactivated gene by p53 to induce cell death in response to genotoxic agents. hNoxa can release cytochrome c from the mitochondria, resulting in activation of caspases; however, the molecular mechanism is largely unknown. Previous report showed that hNoxa contains two functional domains, BH3 domain and mitochondrial targeting domain (MTD). Here we showed that MTD has a dual function; targeting of hNoxa to mitochondria as previously suggested and a cell killing activity by induction of the mitochondrial fragmentation and calcium release. Deletion of MTD in hNoxa failed to localize hNoxa to the mitochondria and to induce the cell death as well. Interestingly, treatment of MTD peptide to HeLa cells causes a large balloon-like alteration of cytoplasmic membrane within 10 minutes after MTD, ultimately causing the cell death. Furthermore, hNoxa induces the mitochondrial fragmentation in HeLa cells, and MTD in hNoxa is sufficient for causing the mitochondrial fragmentation. Facilitation of the mitochondrial fragmentation by hFis-1 increased the cell death induced by hNoxa in HeLa cells, suggesting that the mitochondrial fragmentation is a critical event for hNoxa to induce the cell death. Moreover, calcium concentration in cytosol was increased by MTD peptide, and it is blocked by cyclosporin A, an inhibitor of mitochondrial permeability transition pore. In conclusion, MTD in hNoxa is a novel killing domain that causes the mitochondrial fragmentation and calcium release.

Key Words: HNoxa, MTD, Mitochondrial fragmentation, Cell death, Calcium release