Eur J Gen Med 2004; 1(2): 1-2

REVIEW ARTICLE

DEFINING A PHYSIOLOGICAL ROLE FOR THE TUBULIN TYROSINATION CYCLE

Haitham T. Idriss
Kimmel Cancer Center, Thomas Jefferson University

This paper proposes, based on data from other laboratories, that the physiological function of the tubulin tyrosination cycle is to maintain a check for normal physiological milieu within cells, whereby tyrosine and nitrotyrosine act as markers for normality and abnormality, respectively. Incorporation of nitrotyrosine is postulated to initiate apoptosis to facilitate elimination of abnormal cells.
Key word: Tubulin tyrosination

The tubulin detyrosination/tyrosination cycle is one of the first observed posttranslational modifications of α-tubulin. The modification involves the cyclic removal and re-addition of a tyrosine residues to the c-terminus of α-tubulin by the enzymes tubulin tyrosine carboxypeptidase (TTCP) and tubulin tyrosine ligase (TTL), respectively.

No definite function has so far been attributed to this modification, but the majority of cytoplasmic microtubules consist of tubulin in the tyrosinated form (1). Recently, it has been demonstrated that nitrotyrosine is a substrate for TTL and is irreversibly added to the c-terminus of α-tubulin leading to microtubule dysfunction and cell death (2). A recent study contradicting this observation (3) most likely overlooked coordination between the tubulin assembly/disassembly, tubulin detyrosination/tyrosination and TTL dephosphorylation/phosphorylation cycles.

I propose the physiological function of the tyrosination cycle is a check-point for abnormality in cells, whereby tyrosine and nitrotyrosine act as the markers for normality and abnormality and incorporation of nitrotyrosine initiates apoptosis to eliminate abnormal cells.

Nitric oxide (and nitrotyrosine, a product of a biochemical reaction between NO and tyrosine) is elevated in abnormal cells such as cancer and/or infected cells. I previously hypothesised that cancer cells that are insensitive to the actions of TNF-α, may escape α-tubulin nitrotyrosination-mediated damage of microtubules (4).

Correspondence: *Haitham T. Idriss*
233 S. 10th St., BLSB 904
Philadelphia, PA 19107-5541. USA.
Tel: 215-503 4631
Fax: 215-923 1098
E-mail: hidriss@mail.jci.tju.edu

Recent studies showed that a major aspect of TNF-mediated cell cytotoxicity is the disruption of the cytoskeletal network, including microtubules (5).

Interestingly, inhibition of protein kinases with H-7 potentiated TNF-mediated apoptosis, suggesting that depressed protein phosphorylation enhances TNF-mediated cell killing. Furthermore, microtubule disrupting drugs such as taxol also accelerated TNF-mediated cell-killing and somewhat enhanced the sensitivity of HeLa cells transfected with Bcl2 for apoptosis (5).

I believe this supports the original hypothesis for the following reasons. H7 is likely to suppress the postulated phosphorylation of TTL, thereby preventing tubulin nitrotyrosination. Taxol have been shown to enhance apoptosis and cause hyperphosphorylation of the anti-apoptotic protein Bcl2 by activating protein kinase A, further accelerating cell death (6). This may also induce TTL phosphorylation (7), diminishing tubulin nitrotyrosination as a consequence. Therefore, microtubule damage, whether induced by taxol or mediated by the incorporation of nitro-tyrosinated tubulin seems to lead to apoptosis commensurate with the hypothesis that have been proposed herein. TTL may well turn out to serve an apoptotic role in abnormal cells.

The tubulin detyrosination/tyrosination cycle may therefore serve as a biological sensor of cellular abnormalities using nitrotyrosine as a marker. I postulate, during each cell cycle detyrosination and re-tyrosination occurs through the actions of TTCP/TTL to serve this function. Once a cell becomes abnormal, TTL irreversibly adds nitrotyrosine, leading to microtubule dysfunction and leading to cell death e.g. through non- productive microtubule/ microtubule-motor interaction.

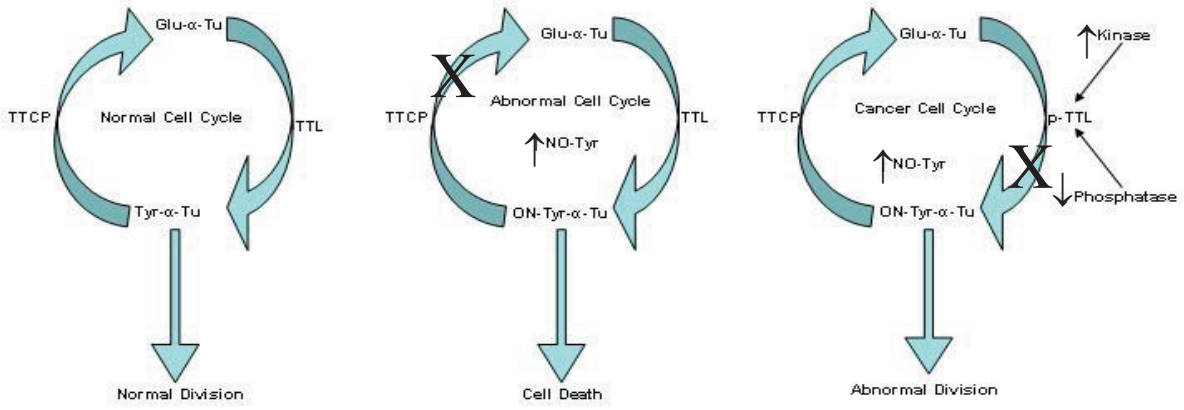

Figure 1. The cell, through the tubulin tyrosination cycle, constantly checks for abnormalities by the cyclic addition and removal of tyrosine or its analogue, nitrotyrosine (NO-Tyr). In a normal cell, tyrosine levels are high and nitrotyrosine levels are low so the cell progresses normally with cell division, utilising a predominantly tyrosinated microtubule network (Tyr-α-Tu). In an abnormal cell (transformed or infected), elevated levels of nitric oxide (NO), lead to elevation of levels of nitrotyrosine, which when incorporated by TTL onto .α-tubulin leads to cell death due to the failure of TTCP to remove this 'abnormal' amino acid and the persistence of a nitrotyrosinated microtubule network (NO-Tyr-α-Tu). In an abnormal cell that escapes apoptosis (e.g. cancer cell), high kinase levels and low phosphatase levels may cause phosphorylation of TTL, thereby inactivating its enzymic activity, such that it is unable to incorporate nitrotyrosine onto .α–tubulin and the cell continues to divide utilising a predominantly non-tyrosinated microtubule network (Glu-α-Tu). It is noteworthy that Okadaic acid, a potent inhibitor of protein phosphatases in eukaryotic cells, is essentially a tumour promoter. Kinase levels (e.g. Protein Kinase C) are increased in cancer cells.

Only when hierarchical suppression of TTL function through phosphorylation, an abnormal cell propagates. This may therefore define the physiological role for the tubulin tyrosination cycle (figure 1). Cancer and/or infected cells most probably escape α -tubulin nitrotyrosination (8).

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