Time to tame necroptosis - viable combat against chemo resistant oral cancer cells

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Till 1998, a little was known about alternative forms of regulated cell death beside apoptosis. In present scenario, accumulating evidences suggest a form of programmed necrosis called Necroptosis which can be induced by various external stimuli including anticancer drugs, ionizing radiation, photodynamic therapy in the form of death domain receptor (DR) engagement by their respective ligands, TNF-alpha, Fas ligand (FasL) and TRAIL, under apoptosis deficient condition (caspase inhibitor), *etc*. receptor interacting protein-1 (RIP-1), a death domain containing kinase is the key molecule in necroptotic cell death pathway. On interaction with an additional protein RIP-3 to form an intracellular complex (complex-IIb), it triggers the various downstream mechanisms of necroptosis which includes: i) excessive production reactive oxygen species (ROS) as RIP-3 interacts with metabolic enzymes (glycogen phosphorylase, glutamate dehydrogenase) which increases the concentration of substrates for oxidative phophorylation - a major source of ROS; ii) mitochondrial dysfunction (mitrochondrial permeability transition). Necrostatin (Nec-1) and CYLD act as negative and positive regulators for this mode of cell death.

TNF the master pro-inflammatory cytokine has been known to either promote gene activation or to induce RIPK1 kinase-dependent cell death, in the form of apoptosis or necroptosis. Autophagy has also been proposed as an execution mechanism for necroptosis.[1,2] There is growing evidence of impairment of necroptosis in tumerogenesis of various human cancers such as chronic lymphocytic leukemia, epidermal cancer and non Hodgkins lymphoma.[2]

As conventional anticancer drugs are usually apoptosis inducers, the development of apoptosis resistant cell clones is inevitable owing to cancer heterogeneity and mutation leading to failure of standard chemotherapy. It is a known fact that triggering necroptosis could be an alternative way to eradicate apoptosis-resistant cancer cells.[3] Development of a new class of anticancer drug targeting this alternative pathway of the cell death is the need of the hour. Few *in vitro* and *in vivo* studies have been conducted showing excellent anti-tumor effect in both drug sensitive and resistant cases by targeting different modulators of necroptotic pathway: i) shikonin-a naturally occurring naphthoquinone showed prompt but profound anti-tumor effect on both primary and metastatic tumor *i.e.* cancer cell lines and osteosarcoma by inducing RIPK1 and RIPK3 dependent necroptosis;[4,5] ii) staurosporine-generally accepted inducer of intrinsic apoptotic pathway and it is a wide spectrum inhibitor of protein kinases. It can induce necroptosis in caspase compromised conditions;[6] iii) deoxypodophyllotoxin - a naturally occurring microtubule destabilizer successfully induced necroptosis in both drug sensitive and drug resistant cancer cell lines;[7] iv) targeting Nec-1, a specific inhibitor of necroptosis can help in inducing necroptosis to enhance the radiosensitivity of cancer cells.[8] Tanshinone IIA (Tan IIA) is known to induces both Nec-1 inhibition and FLIPS regulation-mediated apoptosis/necroptosis;[9] v) obatoclax induces the interaction of p62 with RIP1K, RIP3K and FADD, key components of the necrosome and can mediate cell death in oral squamous cell carcinoma (OSCC) cells via autophagy-dependent necroptosis.[10]

Despite the rigorous implement of conventional therapies, increased number of refractory cases is unavoidable due to acquired resistance of cancer cells, badly affecting survival rate of OSCC. Additional knowledge about the mechanisms of cancer drug resistance and development of novel targeted therapy using alternative pathway of cell death and less susceptible to known resistance mechanisms *i.e.* necroptosis-based cancer therapy may help in designing effective anticancer strategies for OSCC .

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