International Research Journal of Medicine and Medical Sciences
Vol. 1(4), October, 2013
Letter to the Editor

Necrosis and apoptosis in cancer therapy: Nutritional facilitation and irreversible inactivation

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Dear Editor,

Necrosis (Trump et al., 1980) and apoptosis (Kerr et al., 1972; Muntané and De la Mata, 2010) are enzymically-mediated modes of death theoretically available to the cancer cell *in vivo*. Haemorrhagic necrosis in a transplanted mouse sarcoma (Gerber and Bernheim, 1938) is preceded by disruption of energy production, ATP leakage from mitochondria (Jones, 1979) and a precipitous fall in the content of high-energy phosphate bonds (Jones, 1980a). Apoptosis depends on macromolecular synthesis, and is blocked by pretreatment with cycloheximide (Wyllie et al., 1984). This communication considers situations in which cell mortality in cancer treatments may be either facilitated by the provision of factors of dietary origin which are utilised (Mosconi et al., 1989; Jones, 1992) in the process of destruction, or irreversibly blocked by mutagenic procedures.

Necrosis involves at least two enzymic steps. Initially phospholipid undergoes peroxidation. Secondly, hydrolysis by phospholipase A_2 generates lysophosphatides and hydroperoxy fatty acids, which uncouple oxidative phosphorylation (Jones, 1992). The partial protection of interference with L-*iso*proterenol- and hydralazine-induced energy production by indomethacin (Jones, 1980b) in a transplanted mouse sarcoma indicates participation of a polyunsaturated fatty acid in the destructive process (Mosconi et al., 1989). Lower ratios of essential to saturated fatty acids have been reported in the plasma phospholipids of cancer patients; the greatest change was a 48% fall in the linoleic acid content of plasma cholesteryl esters (Mosconi et al., 1989). The total concentrations of w-6 and, particularly, of w-3 polyunsaturated fatty acids were very low in regions of intense cell proliferation in lung tissue from patients with lung cancer (Khyshiktuev et al., 2000).

Apoptosis is more complex. The mandatory need for macromolecular synthesis (Wyllie et al., 1984) is thought to include the synthesis of nitric oxide synthase (Muntané and De la Mata, 2010) and antibodies. In paracetamol poisoning synthase is induced (Gardner et al., 1998; Hinson et al., 1998). Peroxynitrite derived from synthase activity reacts non-enzymically with tyrosine residues in proteins. Toxicity intensifies when alterations in antigenic profiles due to nitration provoke hostile responses from the immune system (Knight et al., 2001). Similar changes occur in the amyloid cascade during the terminal stages of Alzheimer's disease (Smith et al., 1997). Both endothelial and inducible nitric oxide synthase activities are elevated in cancer cells (Muntané and De la Mata, 2010). If tyrosine nitration of cancer cell proteins and the invocation of an immune response are central features of tumour apoptosis, a deficiency of the essential amino acid could compromise the therapeutic outcome.

Under appropriate conditions phenothiazines (Jones, 1985) in low continuous dosage (Jones, 2010b) exert powerful anti-tumour activity; promethazine has shown success in the treatment of an anecdotal series of cancer cases (Jones, 2010a). Dietary supplementation with polyunsaturates is advised (Jones, 2010a, b). Although the initial injury inflicted on tumours by promethazine has been assumed to be necrosis, especially when the phenothiazine is initially given in conjunction with calcium (Jones, 2010b), in the later stages of treatment a limited role for apoptosis cannot be ruled out. Supplementation with tyrosine may be beneficial, as well as in therapies with hormone analogues in which necrosis appears not to feature.

Both necrosis and apoptosis are vulnerable to mutagenic influences, and will be inactivated when genes coding for enzymes essential for the functioning of the mechanisms are deleted from the genome of a single malignant cell. In cancer patients the establishment of cell clones (Jones, 2010a, b) in which both mechanisms are inactivated ensures a fatal outcome.

Keywords: Apoptosis, cancer, polyunsaturates, therapy, tyrosine.

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