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Dimensions of niche-induced anti-apoptosis of therapeutically resistant neoplasm's in radio-chemo-therapy

Abstract

It is proposed that apoptotic linear progression schemes do not adequately account for the emergence of non-response in radio-chemo resistant neoplastic lesions. In such defining contributory patterns of activated and non-activated apoptosis there is emerging evidence for distributional programs sustained by networks of spatial distribution. Such a concept may well implicate angiogenic switches and origins of vessels and tumor cells from a resident stem cell population in the niche micro-environment. It is towards the realization of performance attributes of cell-cycle arrest on the one hand and of proliferative dysfunctionality that the resistance and relapse of tumors is exemplified by an integrated clonogenic phenomenon of cellular derivation and end-result as relapsed neoplasm's.

Keywords: radio-chemo resistant, angiogenic, clonogenic, neoplasms, spatial, micro-environment, clinical, tumor, chemotherapy, anti-cancer, malignant, macrophage, apoptosis, radiotherapy, DNA

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Introduction

The role of apoptosis has traditionally been considered critical in the outcome dynamics of tumor response to cancer therapy. However, there is often considerable discrepancy between the results of short-term tumor cell culture and clinical response to anti-cancer chemotherapy in particular. The tumor microenvironment may possibly be modulated to overcome resistance at sites of checkpoint inhibition.[1] Tumor-associated macrophages support malignant plasma cell survival and induce therapeutic resistance, with up-regulation of M1 macrophage markers.[2]

Central to such considerations is the concept of an apoptosis network functionality and dysfunctionality in response to direct and indirect DNA damage-inducing agents. Oxygen is required in cancer cell destruction by radiotherapy.[3] This implicates multiple pro-apoptotic and anti-apoptotic intermediary mechanisms that essentially modulate therapy outcome. Cancer stem cells are essential in repopulation of different tumors, creating heterogeneous lineages of tumor cells.[4] In such manner, p53 mutations, in particular, are responsible for a propensity for anti-apoptosis in tumor outcome.

Apoptosis networks

The distributional relevance towards the mechanistic processing of energy-dependent apoptosis is related to the further conformational parameters that implicate also cell cycle arrest and variants of apoptosis processes as illustrated by delayed senescence and of post-DNA damage forms of late necrosis. Many signaling pathways in glioblastoma relate to a profile more mesenchymal than epithelial in the presence of an advantageous microenvironment.[5] The microenvironment is an important determinant of colonization.[6]

Further dysfunctionality is illustrated by significant permutations of blocks in the pathway progression dominated by apoptotic cell death in tumors as contrasted by non-neoplastic normal cells. Intra-tumoral heterogeneity occurs within a context at genetic, epigenetic and micro environmental levels.[7] The orthotopic tumor microenvironment is critical to evaluating the clinical significance of new biomarkers in cells or patient-derived samples.[8] Viability or survival clonogenic dynamics are a gold-standard in analysis of tumor cell response to therapeutic agents. Selectivity in target determination is a central issue in cancer therapy and calls to mind the parametric generalizations of network apoptotic initiation and progression.

Combining CXCR4 inhibitors with cytotoxic agents sensitizes leukemic cells with suppression of natural or acquired tumor resistance.[9] The cell-death receptivity's and the intrinsic mitochondrial dynamics in apoptosis are illustrative particularly of an intense interactivity of autonomous and non-autonomous cell reactivity closely linked to the tumor micro-environment. Cancer cells constantly modulate the microenvironment through interactions with immune cells, stromal cells and extracellular matrix.[10]

Apoptosis failure

Failed apoptosis initiation and progression are closely inter-related to mutability induced by DNA damage fostered by anti-cancer therapy. The relative occurrence of accelerated systemic metabolization and insertion of drug efflux pumps within the cell membrane attest for the complexity in delivery of chemotherapy resistance to anti-cancer therapy. Autophagy may in the early stages of cancer be cancer-suppressing, while in established tumors it may promote tumorigenesis.[11]

Mutant or aberrant forms of apoptosis include delayed caspase-independent apoptosis, mitotic catastrophe and autophagy and have been recognized forms of response to anti-cancer therapy and may perform response parametric forms of determined therapy outcome. Persistence of androgens in the prostate microenvironment is a key mechanism by which transition from hormone-sensitive to castration-resistant prostate cancer develops.[12]

Microenvironment

Environmental factors are especially involved in modulating gene expression via epigenetic re-programming without the elaboration of genetic mutations. In such manner radio-chemo resistance may progressively evolve, particularly with relapse of the tumor. Transmembrane CD44 is over expressed in many neoplasm's and is implicated in cell motility, tumor growth and angiogenesis.[13] Non-structural apoptotic mechanisms may implicate functional inhibitory factors that augment tumor resistance to therapy.

Apoptosis is evidenced by phenomena of response by tumors in determining outcome dynamics. The long-term outcome of apoptotic responses is unclear and may be related to niche phenomena in the tumor stem cell micro-environment. Exosomes clearly alter the tumor microenvironment and mediate resistance to therapy, and also promote metastatic spread and immune responses.[14] Oncogenes such as Myc and oncogenic Ras are implicated in ablation of apoptosis pathways and other cell cycle checkpoint-mediated cellular fail-safe mechanisms in malignant transformation.

Multiple pathways of pro-apoptosis are evidenced by cell responses in terms of supra-physiologic DNA damage as revealed by relapsing tumors. Essential accumulation of apoptotic defects would account for global network dysfunctionality in a manner inducing therapeutic resistance, the perforce dynamics of tumor cell turnover in the presence of a rich angiogenesis includes distributional and essential attributes of a phenomenon for outcome performance in apoptosis. The centrality of chemo resistance and of post-radiotherapy relapse attests for modulatory dimensions of niche-derived parameters. Cancer-associated fibroblasts support the growth and spread of melanoma and also contribute to drug resistance, via tumor-stoma interactions.[15] Cancer-associated fibroblasts are important in the initiation and progression of neoplasm's and their suppression may negatively affect cancer progression.[16]

Replication

Replication, including endo-replication, of tumor DNA pathways may prove a central issue in response to radio-chemotherapeutic resistance, with the creation of multinucleated tumor cells that undergo programmed cell death. Tumor cell senescence per se appears a backup phenomenon in those tumor cells that fail to undergo apoptotic cell death.

The significance of discrepancies between apoptosis and clinical tumor outcome indicates the complex relative importance of non-autonomous modulatory effects in niche micro-environmental influence. Nanotechnology advances reduce cytotoxicity, improve circulation in the blood and increase accumulation of therapeutic agents in neoplasms.[17] In this regard, further performance outcomes, especially in terms of mitotic cell division and proliferation, would create permissive conditioning of DNA mutability, on the one hand, and of apoptotic modulation, on the other. Regulatory mechanisms of apoptosis versus non-apoptosis are involved in interactions between dormant breast cancers and mesenchymal stem cells in the bone marrow microenvironment.[18]

Cell cycle arrest

An arrest-delayed repair phenomenon appears to preclude widespread apoptotic cell death, even within the context to attempted therapeutic delivery of chemotherapeutic and radio therapeutic doses. It is within the defining attributes of potential autonomous tumor cell response that niche-induced modulations would perform the emerging roles of tumor relapse. Aspirin may reverse chemo resistance by repressing tumor repopulation by modifying the tumor microenvironment.[19]

Stem cell performance is a central issue that allows for a range of network dysfunctions in relative emergence of radio-chemo resistance. Osteosarcoma plasma membrane acidic pH induces chemo-resistance to different agents.[20] The further co-damage as relative to a rich angiogenesis would allow for resistance clones as illustrated by survival clonogenic assays. The pro-apoptotic cytokine TNF-related apoptosis inducing ligand (TRAIL) may counteract therapeutic resistance by utilizing therapeutic agent delivery by mesenchymal stromal/stem cells in Ewing sarcoma.[21]

Angiogenesis

Such considerations implicate angiogenic endothelial cells as co-factors in therapeutic resistance that induces permissive forms of response when tumor cell DNA is damaged. Hypothetical considerations of a unitary origin outcome for angiogenesis and the tumor cell pool allow for possible interactivities that perform further network distributional patterns of response to therapeutic attempts.

Genetics of adjacent tumor cells call into operative dysfunction the varied patterns for further progression of oncogenesis and malignant transformation. Decellularized matrices may be preferred as cell culture substrates in the in vitro analysis of comprehensive micro environmental chemoresistance.[22] Solid epithelial tumors constitute a particularly resistant target in radio-chemo resistance and would be suggestive of dynamic interactions between different clones of tumor cells, on the one hand, and the active acquisition of further modulatory roles in micro environmental component turnover.

Tumor pathogenesis

Tumors develop from dysregulated and altered malignant cells and their environment; once tissue homeostais is disturbed, a niche may develop to favor tumorigenic transformation.[23] Pathogenesis of malignant transformation is an essential dimensional attribute in the understanding of radio-chemo resistance in a manner that especially involves stem cell biology in the initiation of viability/clonality performance. Non-coding RNAs may regulate altered genes, including apoptosis genes with the establishment of metabolic reprogramming.[24] The further conformational angiogenesis would perform the patterned augmentation of pro-apoptosis and anti-apoptosis realization of resistance phenomena. The overall emergence of interactions between angiogenesis networks and the tumor microenvironment implicate further progression as evolutionary patterns of programmed cell viability.

Concluding remarks

The mutability induced by radio-chemo resistance is paralleled by the DNA-damage as sensor and target agent in activated apoptosis pathways. The further spatial and temporal performance of increments in apoptotic cell death pathways, however, is poorly correlated with clinical tumor outcome in many patients with neoplasm's, particularly in the case of solid tumors. The non-autonomous micro environmental factors, implicating especially epigenetic re-programming may allow for essential network bypass or block in terms that avoid essential apoptosis pathways. A network hypothesis for pro-apoptosis appears

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to better account for radio-chemo resistance than simple unilinear pathways of induced apoptosis. The relevance for further relapse of the neoplasm is well-illustrated by the niche concept of stem cell transformation in modes of incremental dysfunction and genetic damage.

Programs for persistence of the increments in performance also implicate cell cycle arrest and mitotic catastrophe in further agent-induced autonomous tumor cell DNA injury. Programs of patterns of inducible injury, therefore, are simple performance attributes that have to be integrated within other systems of progression as exemplified by rich angiogenesis and mutability issues of clonogenic activity.

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Conflict of interest

Author declares that there is no conflict of interest.

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