

Neosis - A Parasexual Somatic Reduction Division in Cancer

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ABSTRACT We have recently reported a novel type of cell division involved in the origin and growth of cancers. Termed neosis, as opposed to mitosis and meiosis, this type of cell division occurs only in senescent polyploid giant cells and not in normal diploid cells. Up to ~10% of tumor cells *in vitro* and *in vivo*, are polyploid giant cells and so far there is no explanation for their role in cancer. These resemble senescent cells, which are thought to play a tumor suppressor role. We have shown that such cells have the potential to undergo neosis, a parasexual, somatic reduction division characterized by karyokinesis via nuclear budding, followed by asymmetric cytokinesis, (often) giving rise to aneuploid daughter cells termed Raju cells, which are the progenitors of tumor cells. These Tumor Initiating Raju Cells (TIRCs) are unique in that they transiently display stem cell properties, have inherited genomic instability, differentiate into tumor cells and have extended, but, limited mitotic life span (*MLS). At the end of their extended MLS (EMLS), the tumor cells repeat the cycle of senescence, neosis and production of Tumor Rejuvenating Raju Cells (TRRCs), which repeat the same cycle of events several times through the life of tumor in a progressively non-synchronous fashion. When tumor cells are subjected to chemotherapy or radiotherapy, they undergo premature senescence; but, some cells escape senescence via S/T-neosis and yield TRRCs, whose mitotic progenies may be resistant to genotoxins. Although neosis-like events have appeared in the literature sporadically for more than a century under different names, they were neglected since the significance of such events was not known till now. The data on neosis questions the basic tenets of the current concepts of cancer, i.e., (1) Cancer arises via mitosis, (2) Cancer cells are immortal and (3) Cancer cell continuity is due to the unlimited asymmetric mitotic potential of mutant stem cells or Cancer Stem Cells (CSCs). Neosis paradigm supports the concept that (1) Cancer arises via neosis, (2) cancer cells are not immortal, but undergo repeated senescent phases and that (3) tumor cell lineage continuity is due to escape from senescent phase via neosis, since tumor cells carry mutant or epimutant genes in the senescent checkpoint pathway. Thus, genesis and regeneration of Raju cells via repetitive neotic divisions is responsible for the origin and continuous growth of different tumor types. This concept accommodates epigenetic expression of telomerase, meiotic genes, multidrug resistance genes and stem cell-specific genes in tumor cells and also explains the role of senescent cells found in tumor tissues. Thus, neosis appears to involve global epigenetic modulation (EM), in order to fine-tune the chromatin with DNA damage important for producing reproductively viable genomes from the non-viable polyploid genome, before being discarded by post-neotic death of neosis mother cells (NMCs).