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LETTER TO THE EDITOR

Potential role of anastasis in cancer initiation and progression

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Apoptosis is a well-established form of programmed cell death. Although the signaling pathway leading to apoptosis varies largely, the ultimate executors or the effector molecules of apoptosis are the caspases. Once activated these caspases cleave structural proteins ultimately resulting in cell death. Given the gross segmentation of vital cellular organelles noted during apoptosis, the general perception was that apoptosis was irreversible [1]. On the contrary, recent studies have found evidence suggesting that cells which are committed to apoptosis can stabilize and revert back [1–5]. Anastasis is one such pathway wherein after removal of the agent inducing apoptosis, the cells recover to a stable state [5]. Molecular analysis of anastasis has shown similarity to wound healing in the form of upregulated receptor tyrosine kinase, transforming growth factor-β, angiogenesis-promoting pathways and mitogen-activated protein kinase signaling [1]. Like any repair mechanism, a minor population of the recovering cells from apoptosis often carry some form of sub-cellular damage which could reduce the cell's functionality and could even impart a genetic instability leading to oncogenic transformation [1, 4, 5]. To confirm the potential effects of anastasis, researchers must decode the genomic profile of normal cells recovering from apoptosis. In such cells, it is vital to observe if the apoptosis has induced any genetic aberrations which could predispose carcinomatous transformation leading to cancer initiation.

During apoptosis, as detrimental changes are being induced in the form of cell shrinkage, membrane blebbing and apoptotic body formation (Fig. 1), there is a simultaneous accumulation of mRNAs coding for anti-apoptotic and survival factors including the zinc-finger transcription factor Snail [1]. Although these survival coded mRNAs are being accumulated during apoptosis, they are not translated on to the cells until the apoptotic inducing factors subside. These findings provide a clear indication that apoptosis is potentially reversible, although at present it is not possible to predict if the recovering cells would be stable or suffer genetic instability and undergo an oncogenic transformation. In the past, as apoptosis was considered to be irreversible, the common hypothesis was that these stored mRNA will be released following apoptosis and will be utilized by the surrounding cells for their survival and growth. With respect to cancer, it was believed that the surrounding cancer cells could utilize the released mRNA of the apoptosed cancer cells to increase their metabolic activity leading to cancer progression. In contrary, if anastasis prevents cell death, the recovering cells could use its own stored mRNA for recovery and in case of recovering cancer cells, it would serve as an additional energy source for increasing its metabolic, proliferative, and invasive potential. To understand the process of anastasis and its influence on cancer cell behavior, Sun et al. [1] exposed HeLa cells to ethanol (EtOH) for 3 h to induce apoptosis. The EtOH exposure resulted in caspase three activation in 75% of the HeLa cells. After 3 h, the EtOH was removed to allow the cells to recover. Whole-transcriptome RNA sequencing was used to compare the molecular signature of apoptotic, recovering and untreated HeLa cells. Anastasis based revival of apoptotic cells was shown to occur in two phases. In the initial phase, the apoptotic cells which are growth arrested were reverted to a stable state with the

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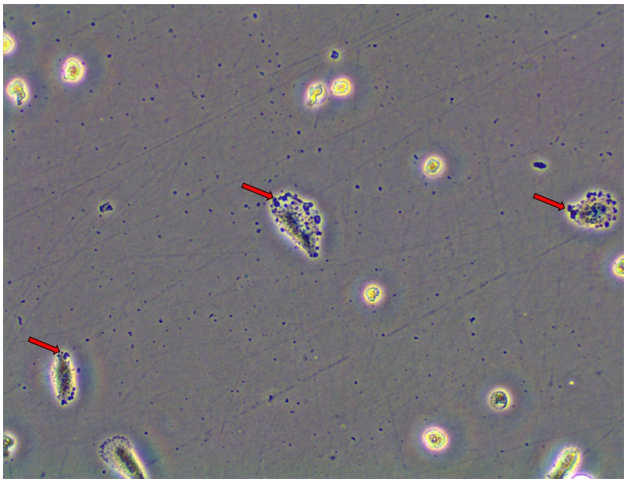

Fig. 1 Cancer cells undergoing apoptosis exhibiting apoptotic body formation (red arrows) (Color figure online)

potential to grow. In the later stage, anastasis increased several tumorigenic properties of the recovered cells including proliferation, epithelial-mesenchymal transition (EMT), migration, and angiogenesis.

Like Sun et al. study on cancer cells, the molecular biology of anastasis in a normal cell should be studied to detect potential molecular aberrations which could predispose the cells to undergo a carcinomatous transformation. In the presence of genetic aberrations, enhancing the apoptotic signals in target cells could overcome its potential for anastasis. With respect to cancer cells, the anastasis could be a survival mechanism against apoptosis induced by therapeutic agents. In such recovering cancer cells, the stored mRNAs could be used to enhance its proliferative, EMT, migratory, and angiogenic properties as elicited by Sun et al. [1]. In addition, any added genetic aberration during anastasis could impart additional therapeutic resistance to the recovering cells. Thus, there is an increased risk of the cells recovering through anastasis to be more aggressive and resistant to therapeutic modalities.

In addition to analyzing normal and cancer cells, future studies must also focus on analyzing the effect of anastasis on stem cells. As stem cells have a longer life span and inherent ability to resist apoptosis, it is more likely that they have a greater potential for anastasis than other cells. Thus, in cancer, targeting the anastatic pathway of cancer stem cells (CSCs) could increase its sensitivity to therapeutic modalities. To conclude, more data is required on anastasis, to understand its potential association with cancer initiation and progression. Future studies must focus on decoding the molecular changes induced during anastasis in normal cells, cancer cells and stem cells (including CSCs). If sufficient evidence is procured suggesting anastasis as a mechanism of cancer initiation or progression, then inhibiting anastasis directly or indirectly through upregulation of the apoptotic signals could serve an effective therapeutic strategy.

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