Chemotherapy-Associated Genomic Toxicity and Future of Cancer Treatment

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Editorial

Cancer genome is usually unstable and, therefore, constantly acquires changes at both the nucleotide sequence as well as chromosomal levels [1-3]. Ongoing genomic changes, which confer new characteristics to the recipient cells, underlie their progression to advanced disease states including acquisition of drug resistance and treatment failure. Data from our laboratory have shown that increased number of mutations correlates with poor survival of myeloma patients [2]. One of the consequences of genomic instability and increased mutational burden can also be the formation of more neo-antigens which help recognition of cancer cells as non-self by immune system. However, continued acquisition of genomic changes can also give new characteristics to cancer cells which may help them escape immune surveillance [4]. Consistent with unstable genome, cancer cells display a number of genomic aberrations including increased levels of spontaneous DNA breaks. Using esophageal adenocarcinoma and multiple myeloma as model systems, we have shown that homologous recombination, the most precise DNA repair mechanism, is dysregulated (or spontaneously elevated) in cancer cells and contributes to ongoing genomic evolution [3,5], drug resistance [3] and growth of cancer cells in subcutaneous tumor model [6]. We have recently also shown that apurinic/apyrimidinic nucleases (APEX1 and APEX2) contribute to increased DNA breaks and homologous recombination activity in myeloma cells [7]. Cancer drugs which are genotoxic or induce DNA damage or breaks, either directly or indirectly, kill cancer cells by increasing the damage to their DNA. However, following such treatments the subsets of cancer cells which survive (and not killed by) as well as normal cells of the patient now have increased levels of DNA damage and breaks. This aspect of chemotherapy poses a risk of development of resistance to treatment in cancer cells and transformation of normal cells. Consistent with this view, we have shown that melphalan, a chemotherapeutic agent, induces homologous recombination activity and genomic instability in myeloma cells in vitro [7]. Similarly, certain chemotherapeutic agents have been linked to development of secondary cancers [8,9]. There are also reports which suggest that chemotherapy has higher likelihood of contributing to development of leukemia as compared to radiation. It is, therefore, necessary to develop drugs which target mechanisms underlying increased genomic damage and instability in cancer cells. Such drugs have potential to inhibit/delay progression by reducing genomic instability and evolution. There is also evidence that such drugs may have ability to increase cytoxicity while minimizing/reducing genomic toxicity caused by chemotherapeutic agents [7].

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