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Targeting drug-tolerant persisters: An alternative therapeutic strategy

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Cancer is the second most leading cause of global deaths next to cardiovascular diseases. Common treatment regimens for cancer include surgery, radiation, and chemotherapy. Despite several advancements, the heterogeneity and complexity of cancer cells make it very difficult to achieve success in treatment. Cancer cells follow several new mechanisms to make the anti-cancer drugs ineffective thereby establishing drug resistance. This results in the need to identify new treatment options and also to explore more on the causes that make cancer cells more evasive and exhibit drug resistance. Recent studies have shown the emergence of a subpopulation of cells after drug treatment called the drug-tolerant persisters (DTPs). This phenomenon was first observed in bacteria. As the name suggests, these DTPs have the ability to remain dormant and tolerate drug shock by undergoing complete epigenetic remodelling. In this condition, as evident from their transcriptomic profiles, the cells exist in a heterochromatin state by keeping only the crucial pathways active for survival and by shutting down the others. These DTPs when subjected to repeated drug shock give rise to resistant populations. It has been observed that the tolerant state is reversible because upon relieving the cells from drug pressure, they tend to go back to their original state by altering their epigenetic conditions. Also, molecules, such as NF-κB, β-catenin, IGF-1G, etc. are known to promote drug tolerance. From existing pieces of evidence, it is well understood that the tolerant state is several steps ahead of resistance, and targeting the cells at this stage would result in a better therapeutic outcome as it eliminates the onset of the resistance phenotype. This can be achieved with the help of epigenetic modifiers. That is, after studying the transcriptomic profile, the chromatin activation states can be understood, and based on the epigenetic modification that is happening in the particular cancer type, a respective epigenetic modifier can be administered to reverse the condition which would ultimately make the cells more sensitive to the actual chemotherapeutic agent. This way, one of the major setbacks associated with cancer therapy can be solved.

Keywords: Cancer, Chemotherapy, Drug resistance, Drug tolerance, Epigenetics

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