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Journal of Clinical Research and Reports

Kaushalendra Mani Tripathi *

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Review Article

Returning to the Hallmarks of Cancer: A Brief Review and Revision

Kaushalendra Mani Tripathi [1*] and Harshit Narula [2]

[1] Graduate Smt. NHL Medical Municipal College, Ahmedabad, India.

[2] Student King George's Medical University Lucknow Utter Pradesh, India.

Corresponding author: Kaushalendra Mani Tripathi, Graduate Smt NHL Medical Municipal College, Ahmedabad, India.

Received date: September 06, 2021; Accepted date: September 15, 2021; Published date: October 02, 2021

Citation: Kaushalendra M. Tripathi and Harshit Narula, (2021). Returning to the Hallmarks of Cancer: A brief review and revision. *J Clinical Research and Reports*, 9(2); **DOI:**10.31579/2690-1919/200

Abstract:

The hallmarks of cancer represent principals and mechanisms on which, different types of cancers function and proliferate, These principals which also include the revised edition include sustained proliferative signaling, Evading growth suppressors , avoiding immune destruction, enabling replicative immortality, tumor promoting inflammation, activating invasion and metastasis, Inducing angiogenesis, genome instability and mutation, resisting cell death, deregulating cellular energetics. This article reviews these hallmarks and suggests any additional hallmark that can be further investigated and integrated into the revised edition , Hanahan and Weinberg's hallmark of cancer are great pillars of understanding for modern cancer study and are open to modification , making it easily approachable ,critiqued and adds the possibility of additions in the near future. The role of exosomes are discussed with the potential to categorize drug resistance as a separate hallmark to assist us in developing therapeutics that can counter or bypass these mechanisms that assist cancer cells to proliferate even further.

Keywords: hallmark of cancer; angiogenesis; tumor; drug; metastasis; lipids; exosome

Introduction

Hanahan and Weinberg's hallmark of cancer sets the cornerstones of modern cancer medicine and research, the current hallmarks described are sustained proliferative signaling, Evading growth suppressors , avoiding immune destruction, enabling replicative immortality, tumor promoting inflammation, activating invasion and metastasis, Inducing angiogenesis, genome instability and mutation, resisting cell death, deregulating cellular energetics. The term hallmarks define mechanisms that facilitate a "microenvironment" that allow otherwise normal cells to replicate, invade and metastasize, given its open ended definition, a hallmark encompasses these points and opens itself to modification and review, with a need to be reviewed every decade or so as further more mechanisms may be discovered or explored but what constitutes a hallmark is agreed upon in my opinion due its broad definition [1].

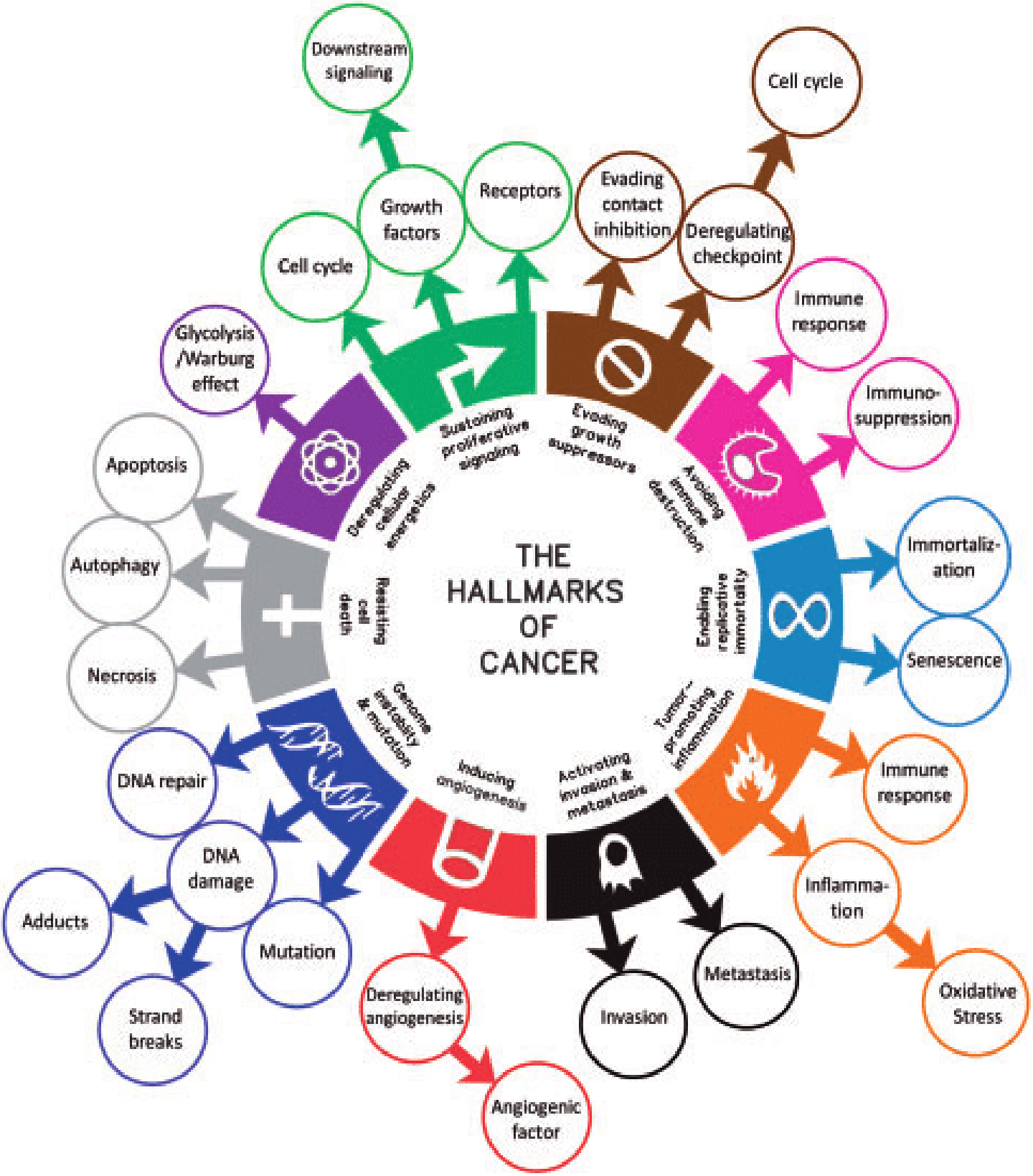

Figure 1: *The image above demonstrates the underlying mechanisms behind every hallmark than can lead to the pathogenesis of a tumor [2].*

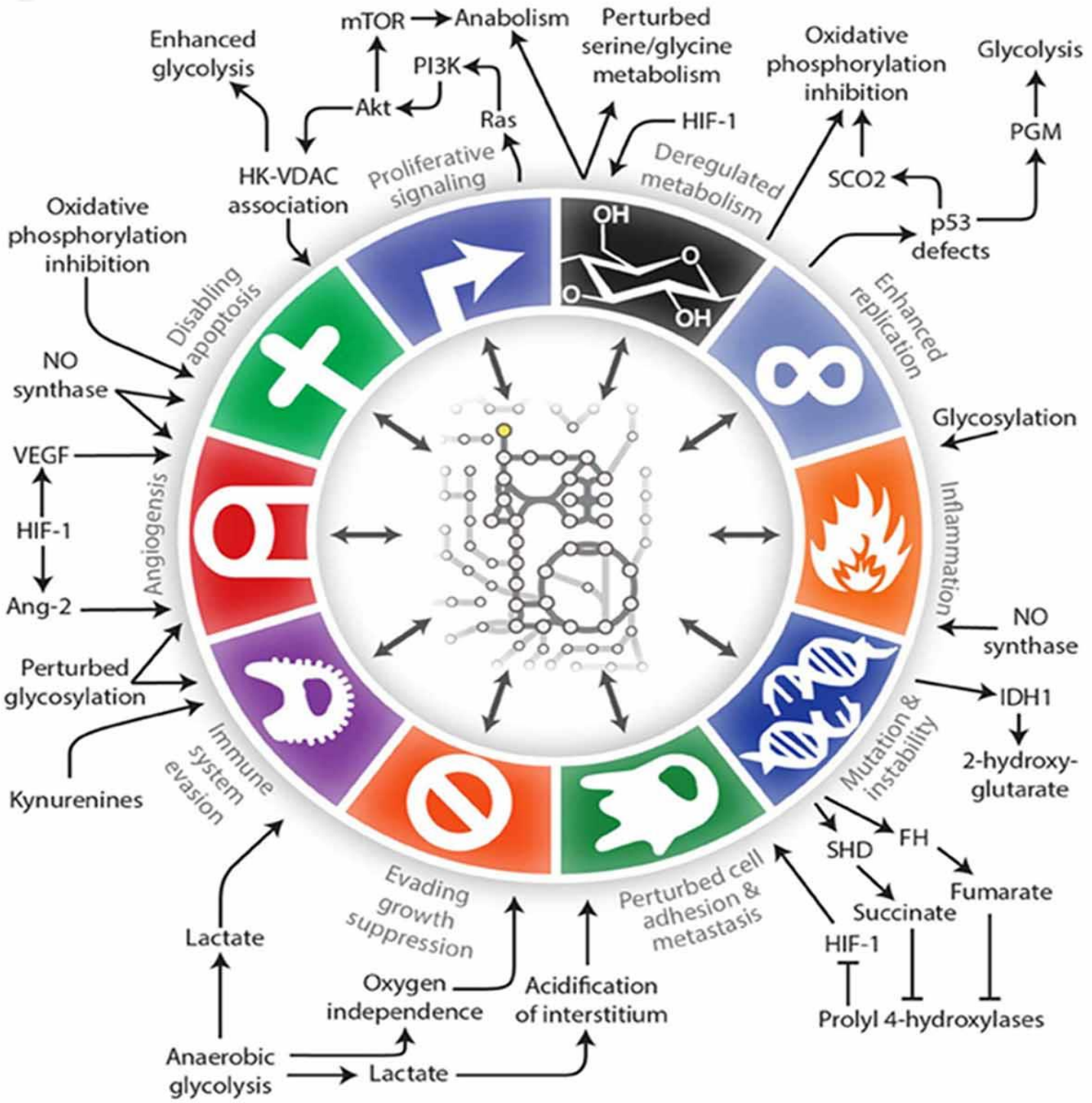

Figure 2: *The hallmarks provide a framework and set of parameters for a variety of cancers and their pathogenesis, as illustrated in this diagram which describes the relationship between tumor metabolism and treatment in "Tumor Metabolism, the Ketogenic Diet and β-Hydroxybutyrate: Novel Approaches to Adjuvant Brain Tumor Therapy" [3].*

Since the hallmarks of cancer are open to reviews and modifications, we will further discuss pathogenesis that may constitute as hallmarks, as new discoveries further evolve our understanding of cancer.

Potential new Hallmarks

Drug Resistance and Cancer Survivability: Though Hanahan and weinbergs articles mention resistance of cancer to drug and internal body mechanisms, this was not clearly elucidated with the role of exosomes, that is why I believe there is a need to separately categorize it and list all related mechanism under such a category. This rises to the standard of a hallmark due to the fact that, this allows the tumor cells to thrive without external or internal factors inhibiting its proliferation. Exosomes are part of a category of intraluminal vesicles (ILV) of multivesicular bodies (MVB) which are 30-100 nm in diameter. An exosome consists of a

variety of complexes, including receptors, transcription factors, enzymes, extracellular matrix proteins, lipids, nucleic acids (DNA, mRNA and miRNA) inside and on the surface of the exosomes. Integrins, tetraspanins, CAMs, MHC class 1 ,2 presented on B lymphocytes and Dendritic cells while transferring and fusion proteins such as e Rab2, Rab7, flotillin and annexin, heat shock proteins such as Hsc70 and Hsc90, cytoskeleton proteins including actin, myosin, tubulin, and proteins such as Alix that mediate MVBs formation belong to non-specific protein types of exosomes. Lipids play an important role in the protection, formation with lysobisphosphatidic acid (LBPA) that is a part of multivesicular bodies (MVB) that lead to the creation of exosomes. Tumor derived exosomes play a role in the modulation and regulation of a tumor microenvironment i.e. the fibroblasts, endothelial cells and infiltrating cells via signals and extracellular matrix through receptor signaling and breaks in cell adhesion formation. Integrins are a characteristic of tumor derived exosomes, leading to the initial pathogenesis of colonization and formation of a pre metastatic niche. Exosomes induce angiogenesis through the VEGF/VEGF receptor signaling, fibroblast growth factor, basic fibroblast growth factor, platelet derived growth factor Beta, tumor necrosis factor alpha, transformation growth factor, Notch pathway that is activated by the delta like 4 protein and interleukin 8 for blood vessels to proliferate. Exosomes induce epithelial to mesenchymal transition (EMT) process with the help of TGF-β, HIF1α, β-catenin, IL-6, annexin A2 caveolin-1 or vimentin and nucleic acids like EMT-inducer miRNAs, with the loss of function of E-cadherin along with cell polarity with gain of N-cadherin, twist, snail and vimentin. The role of exosomes possesses the ability of tumor promotion, migration, invasion and metastasis through MMP2 that degrades ECM, releasing growth factors and invasion, heat shock proteins m S100a9, S100a8, TNF-alpha, alpha-SMA, s100a4, Snail with a decrease in epithelial marks such as a E-cadherin and B-catenin, different proteins have different roles in specific cancers, such as miR-21-5p, miR-100-5p AND Mir-139-5P increasing expressions of MMP-2,9,13 and RANKL in prostate cancer for example, the properties detailed here explains the role of exosomes in the pathogenesis of cancers and tumors , that come under different hallmarks though the role of exosomes were not outlined and elucidated in the original and revised edition of the hallmarks of cancer, also its ability induce cancer resistance to treatment and apoptosis causes its role to be very decisive in cancer research and potential therapeutics. Exosomes possess the ability to pack and transport chemotherapeutic agents, many signaling and antiapoptotic pathways coupled with efflux transporters such a P-glycoprotein transporter induce resistance, exosome-mediated miR-155 induces chemo resistance via EMT markers and targeting TGF-β, FOXO-3a and C/EBP-β mRNA, LncRNA-SNhg14 IN HER2+ breast cancer activates exosome mediated trastuzumab resistance by its action on the BCL2/BAX signaling pathway. Human ovarian carcinoma with cisplatin (CDDP) demonstrated exosomal malformed protein sorting causing CDDP export, exosomes possess the ability to modify signaling pathways such as MTORC, PTEN,MPI3K/AKT and EGFR leading to resistance in chemotherapies, exosome use decoys that evade an immune response, antibody based drugs are also neutralized by tumor derived exosomes , an example of a decoy is the exosomal CD20 receptor that intercept the CD20 antibody decreasing the efficacy of the drug, Her2 breast cancers confer trastuzumab resistance by secreting exosomes that contain TGFb1 that immunosuppresses and inhibit PDL1 the lymphocyte activation inhibitor [4].

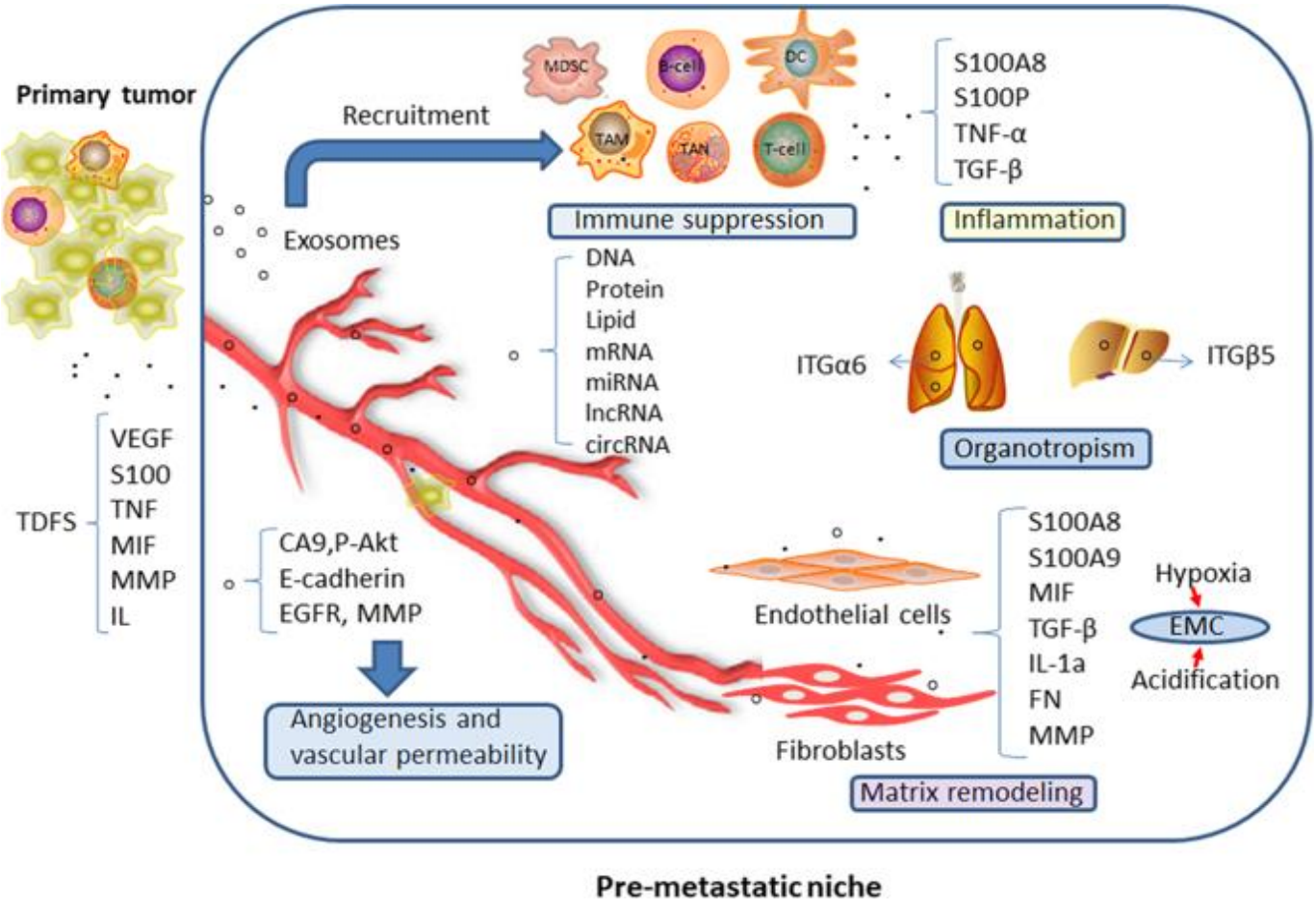

Figure 3: *Brief summarization of the role of exosome (5)*

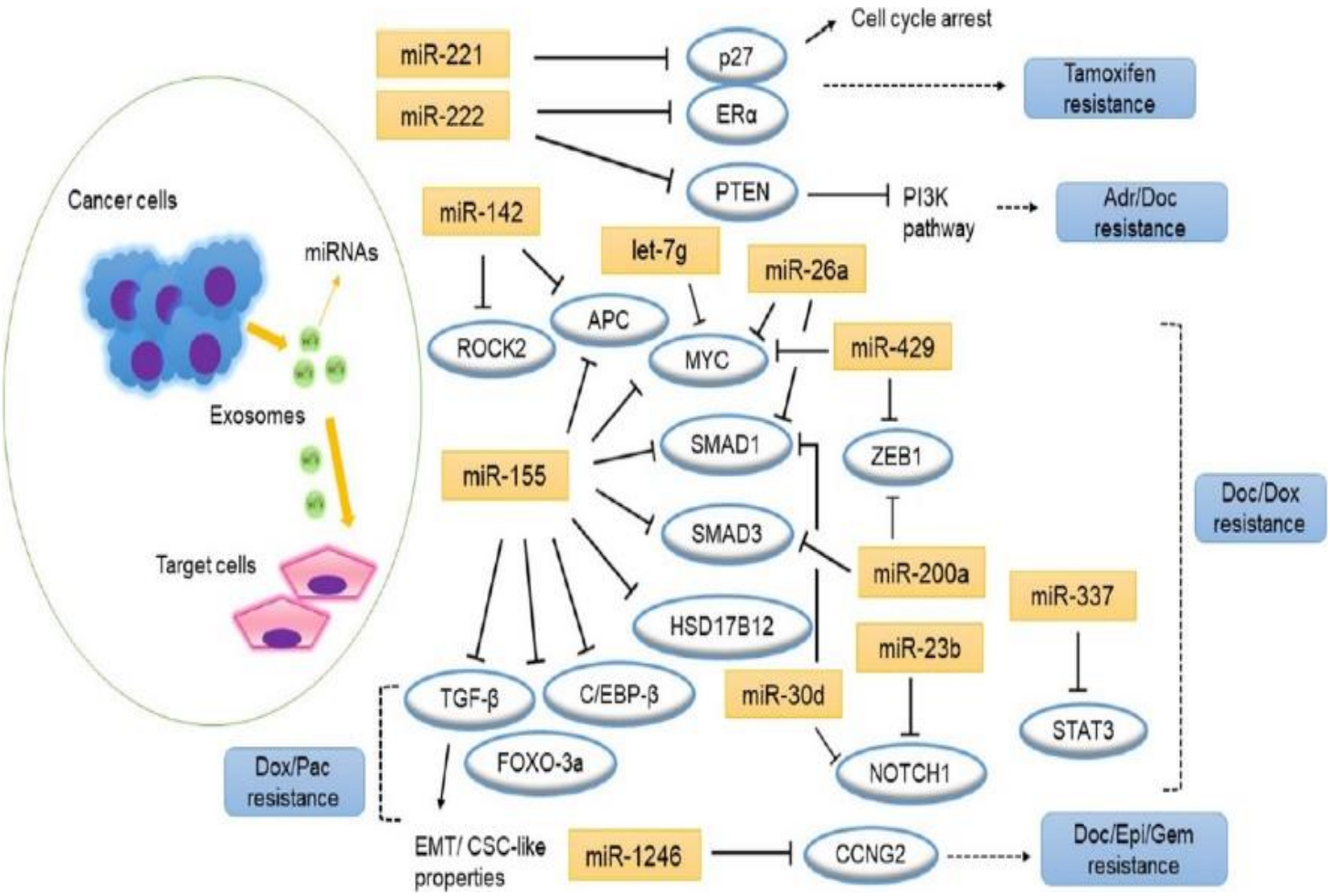

Figure 4: *An example demonstrating signaling pathways involved in the drug resistance from breast cancer cells [6]*

Conclusion

In conclusion the role of exosomes that is relatively new can be further studied leading to a further development in chemotherapeutics and further understand how to counter the resistance cancer develops, due to effects such as repair of DNA damage, apoptotic inhibition, Epithelial to mesenchymal transition, cell heterogeneity , epigenetic effects or even external factors due to drug interactions and action of CYP450 enzymes, there is a need for the development of regimens that counter these effects and prevent potential relapse in cells, in patients with remission, there is a need to counteract these systems , in conjunction with potential improvements in the understanding of the hallmarks of cancer which are subject to critique, possible additions and improvements, epigenetic drugs possess the ability to desensitize drug resistant cancer cells, with exosomes playing an important role in the metastatic niche and have the potential to serve as biomarker in the prognosis of cancer, metastasis prediction and tumor diagnosis due to their role in the survivability and resistance of cancer to factors that destroy cancer, there is a definite need for improvement in treatment regimens that can counter resistance in these cancer cells and the current protocols mention the use of combination therapy to prevent drug resistance, there is also a necessity to target progenitor cells which are the origins of drug resistant cells [7].

Summary

In summary there is an emphasis on the need to understand and apply knowledge from the hallmarks to counter cancer at different levels, the hallmarks are subject to constant modifications if need be and extensively study exosomes to help further develop therapeutics to counter the possibility of drug resistance in cancer , a separate hallmark to explain the resistance cancers helps us further develop treatments to target or counter such mechanisms that may otherwise be difficult to delineate if mentioned under other hallmarks.

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DOI: 10.31579/2690-1919/200