Combining EP4 prostanoid receptor inhibition with photothermal therapy for effective treatment of cervical cancer

Sheetal Parida

Roll no. 11MM91F01

According to Global cancer facts and figures, 2015, cervical cancer was fourth most commonly diagnosed cancer in women in 2012 and India accounted for 25% (67,500) of cervical cancer deaths. PGE-2 is significantly up-regulated in cervical cancer and *via* prostanoid receptor EP4 stimulates proliferation, angiogenesis and motility while inhibiting apoptosis and immune surveillance. We demonstrated combination of GW627368X, a highly selective competitive EP4 antagonist with gold nanorod mediated photothermal therapy for effective treatment of cervical cancer. To begin with, our preclinical study on mouse sarcoma model ensured anti-tumor potential and safety profile of GW627368X deeming it suitable for further study. In cervical cancer, GW627368X inhibited proliferation and induced apoptosis by disrupting EP4/EGFR cross-talk. GW627368X reduced PKA phosphorylation, in turn, decreased CREB activation, enhanced Bax activity and reduced GSK3β phosphorylation. GW627368X lowered EGFR phosphorylation in turn reducing Akt, MAPK and GSK3β, β-catenin activity. Decreased CREB and β-catenin transcriptional activity restricts aberrant transcription of key genes like EP4, COX-2, VEGF and c-myc. Reduced EGFR enhanced 15-hydroxyprostaglandin dehydrogenase expression, thus, increasing PGE-2 degradation. Further, we designed a unique, gold nanorod embedded block copolymer micelle loaded with GW627368X to achieve targeted drug delivery and photothermal therapy simultaneously. The diblock copolymer formed self- assembled micelle around gold nanorods which was loaded with GW627368X. Due to folic acid targeting moiety, drug loaded nanoparticles aggregate in and around cancer cells. High glutathione concentration degrades the micelle and releases the drug to induce apoptosis. When incident with cwNIR lasers of 808nm wavelength, gold nanorods induce photothermal effect leading to rapid rise in temperature and hyperthermic cell death. In response to photothermal treatment, the cells undergo a regulated, patterned cell death via necroptosis. Combination of GW627368X nanoformulation followed by photothermal treatment greatly enhanced therapeutic efficacy. Lastly, we employed the combination of photothermal therapy and targeted delivery of GW627368X to counter cisplatin resistance in cervical cancer. Necroptosis induced by phototehrmal therapy could be utilized as an

alternate pathway to ablate cisplatin resistant cervical cancer cells which are intrinsically resisrant to apoptosis. Additionally, combining PTT with targeted delivery of GW627368X greatly enhanced therapeutic response.

Keywords: Cervical cancer, GW627368X, Photothermal therapy, Apoptosis, Necroptosis