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Inosine 5'-monophosphate dehydrogenase (IMPDH) as an anticancer target: Renewed interest and recent progress

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IMPDH is an enzyme required for the *de novo* synthesis of guanine nucleotides. IMPDH inhibitors have found their usefulness as anticancer, antiviral, immunosuppressive, antimicrobial agents, etc. Despite being an old target, there is renewed interest in IMPDH inhibitors as anticancer agents. Several classes of inhibitors have been reported as anticancer agents. The talk will summarize the molecular details of IMPDH as a target and the recent progress made in the design and development of IMPDH inhibitors as anticancer agents, with particular emphasis on the computer-aided molecular design of the inhibitors.

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Role of IGF-1R/PIK3CA/Akt signaling in acquirement and maintenance of chemo-resistance in ovarian carcinoma

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Worldwide in both developed and developing countries, ovarian cancer patients meet the same challenges: late diagnosis of the disease and acquirement of resistance towards chemotherapy. Thus even with improved management of this disease, mortality rate (>25%) remained same for past two decades. In absence of a standard targeted therapy, platinum-taxol combination treatment has emerged as a primary therapeutic therapy for advanced stage ovarian cancer patients. In spite of promising initial response, majority of these patients acquire drug resistance within 1-2 years and finally succumb with the relapsed disease. Therefore, it is imperative to understand the molecular course of resistance development and identify probable therapeutic targets for ovarian cancer. Using various chemo-resistant cellular models, my lab is engaged in understanding the influence of insulin like growth factor receptor 1 signaling (IGF-1R) and modulation in p53 binding to PIK3CA gene promoter during acquirement of resistance. We show that cells purposely up-regulate the IGF-1R expression at the early stage of resistance to cope up with the stress imparted by the drugs (either cisplatin or paclitaxel or combination of both). Interestingly, up-regulation of IGF-1R expression after chemotherapy treatment was also observed in a small group of patients accrued in a longitudinal follow up study. Combinatorial treatment of IC10 and IC20 doses of drugs (cisplatin/paclitaxol/Cis+Pac) with IC10 and IC20 doses of Picropodophyllin (PPP), a small molecule inhibitor of IGF-1R, sensitized (~20-30% more) these early resistant cells towards treatment. Our study also shows that IGF-1R expression is dispensable at late stages when the cells become highly resistant. At that point Akt, a downstream effector molecule of IGF-1R signaling takes control and maintains resistance possibly through NF-kb and Bcl2 (at least in cisplatin resistant cells. Interestingly, in these late resistant cells Akt acts as a suppressor of IGF-1R indicating a feedback loop in the IGF-1R/Akt pathway during development chemo-resistance. Combinatorial treatment of IC10 and IC20 doses of cisplatin or paclitaxel or both drugs with IC10 and IC20 doses of PPP do not efficiently reverse resistance in these late resistant cells. However, such combinatorial treatments of drugs with IC10 and IC20 doses of an Akt specific inhibitor induce 30-40% more cell death in late resistant stages. In another study, we find that p53 when activated by cisplatin or paclitaxol treatments acts as an attenuator for PIk3CA promoter activity in chemo sensitive cells. Using two different luciferase reporters and non-invasive molecular imaging, we also show that cisplatin treatment induces p53 activation and PIK3CA attenuation simultaneously in same tumor xenografts. Intriguingly, binding of p53 on PIk3CA promoter is observed to be lost/ reduced in chemo-resistant cells probably due to alteration in post translational modifications in p53. All together our data indicates that an intricate interaction of IGF-1R/PIK3CA/Akt signaling components promote and maintain chemo-resistance in ovarian cancer cells. It is thus possible to sensitize the resistant cells towards chemotherapy along with targeted inhibitor only after a careful assessment of resistant stages and expression status of IGF-1R or Akt.

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