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A small molecule inhibitor to overcome the effects of chemotherapy induced stem cell loss

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Introduction

Discovery of a new lead compound PUMAi came up with a novel turning point in chemotherapy induced lethality in increasing the life span of colon cancer patients followed by a drug treatment. The small molecule inhibitor of PUMA (PUMAi) is a highly efficient molecule that prevents chemotherapy induced intestinal injury during p53- dependent apoptosis. It causes drastic decrease in the active caspase-3 levels to induce apoptosis in cryptic bottom cells (CBCs) after treatment. This study reveals the achievement of intestinal chemoprotection by selective inhibition of PUMA and injury induced apoptosis, without influencing the protective effects from the key regulator of damage response. Mediators of p53 are targeted or knocked down to protect against CPT-11 (current chemotherapy drug in use) induced lethality in cancer patients. *puma* KOs had enhanced survival rates indicating inhibition of CPT-11 induces dose dependent lethality. They hypothesized that the Wnt and NOTCH pathways could activate LGR5+ stem cell loss to further deplete the remaining LGR5+ with CPT-11. Hence, the activation of PUMA mediated apoptosis is inhibited by PUMAi and *puma* KOs through Wnt and NOTCH pathways in order to overcome the loss of LGR5+. Their results conclude the PUMAi as an efficient compound in targeting LGR5+ from depletion. Understanding the pharmacokinetics properties of PUMAi would help in enhancing the survival rates of colon cancer patients with the discovery of new analogs of PUMAi.

Colorectal cancer (CRC) is among the leading cause of death and is responsible for 694,000 deaths annually worldwide.[1] A gradient of signaling pathways are involved with colon, in which Wnt (wingless-related integration site) and NOTCH are the highly influenced pathways in colon cancer cells that function together to bring in self-renewal and proliferating abilities of the colon crypts. [1] A tumor suppressor gene, adenomatous polyposis coli (APC) controls the levels of β-catenin which is a downstream effector of Wnt pathway. Loss of APC control of β-catenin causes hyperactivation which causes CRC progression. [2] CPT11 is the current chemotherapy drug which is used in combination with 5-FU (fluorouracil) to treat CRC. Repeated cytotoxic treatment for CRC leads to enterotoxicity caused by the accumulation of SN-38 (an active metabolite of CPT-11) directing to apoptosis of cryptic bottom cells or CBC of intestinal stem cells (ISC). The activation of the damage regulator p53, promotes the action of PUMA (p53 upregulated modulator of apoptosis) which is a downstream effector of the p53 activation pathway to provoke chemotherapy induced intestinal injury. [3]

PUMA is one of the BH3-only protein [4] in the intestinal epithelium that becomes sensitive when exposed to radiation therapy, which leads to radiation induced apoptosis occurring through mitochondrial pathway to cause mitochondrial dysfunction. Transmission of the death signal to mitochondria through PUMA by the activation of Bcl-2 family members (Eg: BAX, BAK), produce active apoptogenic mitochondrial protein cytochrome c, to induce caspases and apoptosis (Fig.1). While p53-dependent PUMA induction has a negative outcome in chemoprotection, PUMA depletion has little detrimental effects in colon cancer patients. Thereby, the effect of suppressing the expression of PUMA can be used as a potential target against radiation induced acute enteropathy. [5] The paper, Leibowitz *et al.* [3] illustrates the major DNA damage regulators'(p53) role in apoptosis of intestinal cells after chemotherapy and to find a way to safeguard the ISCs without compromising the antitumor activity. This was done with *puma* KOs or PUMAi to serve as a protection mechanism against the loss of $LGR5^+$ stem cells (a biomarker of adult stem cell which is also a target of Wnt pathway) leaving behind the p53- dependent protective effects against cancer. They discovered 'PUMAi', a small lead compound to knockdown the activity of the PUMA protein *in vivo,* to aid in protection against repeated CPT-11 induced lethality.

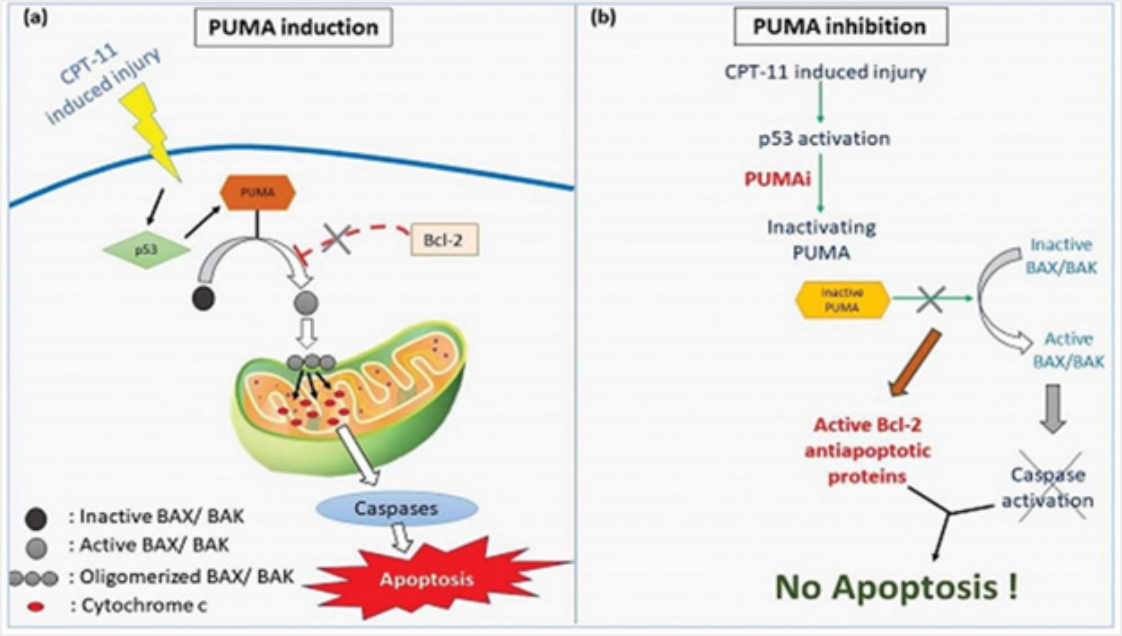

Figure 1: The downstream cascade of PUMA effector during activation by injury and PUMA inhibition by PUMAi: (a) During activation of PUMA, Bcl-2 anti-apoptotic proteins are inhibited to induce pro-apoptotic protein to undergo apoptosis. (b) Upon inhibition of PUMA, anti-apoptotic proteins become active. Hence, it prevents cells from apoptosis.

Leibowitz and his colleagues compared the wildtype (WT) mice with p53 and *puma* KOs, to investigate the consequences of PUMA induction in CPT-11 induced lethality and crypt apoptosis. RNA *in-situ* hybridization results provided strong evidence for the absence of lethality effects after chemotherapy in *puma* KOs. The rate of survival of *puma* KO mice with increasing dose of CPT-11 was consistent with the previous findings by the authors of the current study, which showed that CPT-11 induces dose dependent lethality in WTs and to have higher rates of survival in *puma* KOs. Also, the decrease in rates of survival in p53 KOs gave evidence for the lethality when knocking down the damage regulator pathway. The authors identified a small molecule called PUMAi which is highly efficient in reducing the active caspase-3 levels to induce apoptosis in CBCs after treatment. Leibowitz *et al*. carried out a pharmacokinetic experiment to investigate the distribution of PUMAi in CBCs through high-performance liquid chromatography. The results suggested PUMAi to have fairly a good half- life within the intestinal mucosa even after several hours of treatment, with low concentration of PUMAi detection in plasma. These exciting results confirmed the specific targeting of the damage responsive pathway of p53 to greatly diminish the post treatment lethality. [3] Another study done by Jiang *et al* [6] in *Drosophila* explains that multiple signaling pathways are cross regulated in maintaining ISCs depending on the specificity of tissue. However, the knowledge is still lacking on how the niche signals are regulated to control ISC during regeneration after the treatment induced injury in mice. By using the constructed LGR5-EGFP reporter system in mice, the sheltering of the LGR5$^+$ SCs from damage was studied and it gave a supporting result to previous findings of this paper. Both PUMAi and *puma* KOs decreased apoptosis of LGR5$^+$ cells drastically followed by the treatment which supported their hypothesis ("signaling of the CBC loss is via niche emptying"). [3]

The effect of tumor response in relation to the weight loss after CPT-11 treatment, was analyzed with Lewis lung carcinoma (LLC) tumors and PUMAi in mice. As for *puma* KOs, PUMAi treated cell lines also showed a higher resistance to weight loss. This was also true for the effects on proliferation and apoptosis. CD166, a biomarker of colorectal stem cells, is present in crypt-based paneth cells which is specific for intestinal cancer. Earlier studies done by other authors iterate the role of CD166 in cancer progression. [7] PUMAi and *puma* KOs were identified to largely suppress CPT-11 induced expression of WNT and NOTCH responsive genes which are involved in the expansion of cancer cells. Also, they hypothesized that LGR5$^+$ loss by activated Wnt and NOTCH pathways could further deplete the remaining

LGR5$^+$ with CPT-11. PUMAi and *puma* KOs can overcome the loss of LGR5$^+$ as a result of the abovementioned signaling pathways by inhibiting the activation of PUMA mediated apoptosis. These results conclude that PUMAi is efficient enough to target LGR5$^+$ from depletion. Another question which they wanted to find answer to is whether the action of PUMAi is directly on crypt cells of CBCs or not? Using a three- dimensional model of epithelial organoid, they investigated role of PUMAi in suppressing the

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activation of caspases. Activated WNT and NOTCH signaling genes in response to CPT-11 promoted intestinal injury was repressed by the activity of PUMAi. Increased organoid growth followed by PUMAi treatment strongly emphasized the translational potential of PUMAi [3]

Apart from the action of PUMAi on targets of the mentioned signaling pathway, they identified a significant difference in the levels of activity of PUMAi between species (human and mice in this case) and between the organoids of these species. Wnt agonists and some growth factors do have an important role in preserving the $LGR5^{+}$ from loss. The study as a whole provides clear evidence of targeting or knocking down the p53 mediators without p53 itself to protect against CPT-11 induced lethality in cancer patients. This paper highlights some important questions for further studies. The authors discovery of a new lead compound PUMAi came up with a novel turning point in chemotherapy induced lethality which had a great impact on the life span of the colon cancer patients after the drug treatment. It will be fascinating to see the effects and other targets of PUMAi during various types of tissue or organ injury involving inflammation and DNA damage as it has not been discussed in their present work. Further studies are also needed to identify the kinetics and mechanism of action behind the small molecule inhibitor PUMAi to understand in depth its detrimental effects when blocking the PUMA mediated apoptosis, which the paper failed to discuss. Considering those pharmacokinetics properties would help to design new analogs of PUMAi to treat lethal tissue or organ related injuries way better than PUMAi and to increase the rate of survival of cancer patients.

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