S.V.1.

Type II transglutaminase regulates ΔNp63α level to control epidermal squamous cell carcinoma stem cell survival

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We have recently shown that transglutaminase 2 (TG2) is a key controller that is required for epidermal squamous cell carcinoma cancer stem cell survival. These epidermal cancer stem cells (ECS cells) fail to thrive following TG2 is knockdown. Moreover, ECS cell survival requires TG2 GTP binding activity, but not the transamidase activity. However, the molecular mechanisms that interact with TG2 to control ECS cell survival are not well understood. In the present study we examine the role of the canonical keratinocyte differentiation/survival regulator, ΔNp63α, as a mediator of TG2 action. We show that knockdown of TG2 results in reduced ECS cell survival and this is associated with reduced ΔNp63α level. However, ΔNp63α knockdown does not reduced TG2 level. Moreover, expression of ΔNp63α expression in TG2 knockdown cells restores ECS cell survival. These studies suggest that TG2 controls ΔNp63α level as part of a pathway that controls cancer stem cell survival. We will also discuss the impact of sulforaphane, a diet derived cancer prevention agent from broccoli, on TG2 and ΔNp63α level, and the implications for sulforaphane use as an agent to prevent skin cancer.

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S.V.2.

Challenges and success in basal cell carcinoma chemoprevention by small molecule silibinin

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Basal cell carcinoma (BCC) is the most common non-melanoma skin malignancy worldwide, and its incidence is rising at an alarming rate due to several factors; solar ultraviolet radiation (UV) exposure out of recreational activities being the major one. BCC has abnormalities in hedgehog pathway resulting in constitutively active hedgehog signaling. Typically, BCC tumors harbor a mutational inactivation of tumor suppressor patch gene or activating mutations in smoothened, together with p53 signature mutations. Notably, between sun exposure and the development of BCC and squamous cell carcinoma (SCC, another non-melanoma skin cancer form), there is a significant amount of time (50–55 years), which offers a unique opportunity to intervene with chemopreventive agents. Importantly, whereas chemoprevention has been extensively studied as a practical modality to control and manage various epithelial malignancies; currently no chemopreventive treatment options are available to BCC patients. Several studies have attempted to address this issue showing little to no effect against BCC in the clinical phase, highlighting the need for better preventive strategies for this most frequent human malignancy. In our laboratory, silibinin, a small molecule flavonoid isolated from the seeds of milk thistle, has shown promising effects against UVB radiation-induced skin cancer of squamous origin. Based on the belief that at least some of the etiological mechanisms of BCC and SCC are common, in our ongoing recent studies, for the first time, we focused our attention on assessing the efficacy and associated mechanisms of silibinin against BCC in both cell culture and animal models. Completed studies found that indeed silibinin has strong efficacy in inhibiting growth and inducing apoptotic death of a panel of BCC cells of murine and human origins by targeting multiple signaling pathways in both cell culture and an ectopic allograft model. This suggests the need for additional efficacy studies with silibinin in pre-clinical and clinical BCC chemoprevention and therapy models.

Key words: Basal cell carcinoma; chemoprevention; phytochemicals; silibinin; dehydrosilibinin; mitogenic signaling; EGFR

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S.V.3.

Redox signaling in cancer prevention by dietary phytochemicals

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The past few decades have experienced remarkable progress in identification and preclinical characterization of cancer preventive phytochemicals from edible and medicinal plants. Examples of highly promising cancer preventive phytochemicals primed for clinical investigation in not so distant future include benzyl isothiocyanate from cruciferous vegetables and withaferin A (WA) from a medicinal plant (*Withania somnifera*) to name a few. These phytochemicals are structurally different but share common mechanism of action due to presence of thiol-reactive chemical side chains. This presentation offers novel insights into the role of redox signaling in cancer prevention by these phytochemicals. Examples of common mechanistic targets (functional role) of electrophilic cancer protective compounds include mitochondrial respiratory chain complexes (apoptosis due to production of reactive oxygen species) and tubulin (mitotic arrest).

Key words: dietary phytochemicals; isothiocyanates; withaferin A; chemoprevention

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S.V.4.

Antiproliferative effects of cyclopentenone prostaglandins in highly metastatic osteosarcoma cell line

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Osteosarcoma is one of the most common malignancies of childhood which accounts for 20% of primary bone cancers in patients under 20 years of age. Aggressive surgical treatment combined with chemotherapy has not improved the average 5-year survival rate of 60%. The major clinical problem is resistance to chemotherapy as observed in many osteosarcoma patients. That is why it is of critical importance to investigate new drugs which would potentiate apoptotic and necrotic response to standard chemotherapy. Prostaglandin 15-deoxy-delta(12,14)-J2 (15d-PGJ2) is an endogenously synthesized thiol-reactive cyclopentenone derivative known for exerting pleiotropic effects in the cell, among others, anti-inflammatory, antiviral and antiproliferative ones. However, the molecular mechanism has not been elucidated. In our experimental model based on the highly metastatic osteosarcoma 143 B cell line, we observed antiproliferative and proapoptotic effects of prostaglandin 15d-PGJ2 with a thiol-reactive 2-cyclopenten-1-one ring in the structure, as opposed to other prostaglandins and prostaglandin derivatives which lack this characteristic structural motif. Our preliminary results suggest that 2-cyclopenten-1-one covalently modifies sulfhydryl groups (Michael addition reaction) on proteins and biologically important peptides involved in oxygen defense mechanisms, and thus being responsible for the upregulation of intracellular level of oxidative stress. Flow cytometry analyses confirmed that the mechanism of 15d-PGJ2-induced cell death was associated with increased generation of reactive oxygen species (ROS) in osteosarcoma 143 B cells. Surprisingly enough, 2-cyclopenten-1-one alone did not show similar deleterious effects in our biological model which may suggest that the efficacy of the Michael reaction in biological system depends, at least to some extent, on the hydrophobic interactions stabilizing 2-cyclopenten-1-one in the vicinity of the reactive cysteine thiolate. Our results allow to propose 2-cyclopenten-1-one as a base structure for chemical synthesis in quest of anticancer drugs which would be more effective in both osteosarcoma treatment and prevention of tumor recurrence.

Key words: cyclopentenone; prostaglandin; osteosarcoma; reactive oxygen species; cell death

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