Index no: 104/19/Life Sc./26

Title:

Therapeutic effect of microbial proteases in Protease-activated receptor (PARs) induced apoptosis in ovarian cancer cells

Abstract

In pursuit of isolating novel anticancer proteases from environmental microbial isolates, we have purified and identified an extracellular metallo-protease from *Bacillus altitudinis* named **Peptidase M84**. This protease selectively triggered apoptosis in human ovarian adenocarcinoma cells (PA-1, SKOV3) and mouse ovarian carcinoma cells (ID8), in addition to exhibiting no significant effect on normal human epithelial ovarian cell (IOSE) and mouse peritoneal macrophage (PEMΦ) cell viabilities. **Protease activated receptor-1 (PAR-1)**; a GPCR which is reported to be overexpressed in ovarian cancer cells was identified as a novel target of Peptidase M84. We observed that Peptidase M84 induced PAR-1 overexpression along with activating its downstream signalling effectors NFκB and MAPK to promote excessive reactive oxygen species (ROS) generation in ovarian cancer cells. This disrupted mitochondrial membrane potential, allowed the cytosolic release of mitochondrial cytochrome c, increased the Bax (pro-apoptotic) to Bcl-2 (anti-apoptotic) ratio and promoted DNA damage to evoke apoptotic death of the ovarian cancer cells. Peptidase M84 also reduced nuclear ki-67 expression in these malignant cells to render an anti-proliferative role. In *in vivo* set-up, weekly intraperitoneal administration of Peptidase M84 (12 µg/kg body-weight) in the ID8 mice model significantly diminished ascitic fluid accumulation through induction of oxidative stress, increasing murine survival rates by 60%. Collectively, our *in vitro* and *in vivo* findings suggested that Peptidase M84 triggered PAR-1 mediated oxidative stress to act as an apoptosis inducer in ovarian cancer cells. This established Peptidase M84 as a promising drug candidate for receptor mediated targeted-therapy of ovarian cancer.

Keywords: Microbial protease, Peptidase M84, PAR-1, ROS, Oxidative stress, Apoptosis, Ovarian cancer

Forwarded

31/07/2024

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