Croucher Summer Course 2016
Advances in Immunology in Health and Disease

Ronald
CWK

16-20 August 2016
The University of Hong Kong

Sponsored by: The Croucher Foundation
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The University of Hong Kong

Croucher Foundation
裘槎基金會

18 August 2016 (Thursday) – Day 3

Venue: Rooms G-04-05, G/F, HKJC Building for Interdisciplinary Research,
5 Sassoon Road

Moderator: Prof Z Chen

09:00 – 10:30	**Immunotherapy: The fourth pillar of cancer treatment** Prof T Mak
10:30 – 11:00	**Regulatory cytokine IL-35 in allergic and autoimmune disease** Prof CK Wong
11:00 – 11:20	Tea break
11:20 – 12:50	**The role of cell signalling / cell death molecules in shaping the immune response to infection** Prof M Pellegrini
12:50 – 14:00	Lunch and poster viewing (II) (10 posters) – *Appendix I*
	Oral presentations of selected participants (6 presenters) (10 minutes presentation + 5 minutes discussion)
14:00 – 14:15	1) Dr WANG Xiaohui
14:15 – 14:30	2) Mr ZHANG Xiaoyu
14:30 – 14:45	3) Miss LIU Zhen
14:45 – 15:00	4) Mr WANG Jianzhang
15:00 – 15:15	5) Dr HUTCHINSON Ryan
15:15 – 15:30	6) Dr TAM Chun Yee Rachel
15:30 – 16:00	Tea break, poster viewing and discussion (II) continue
16:00 – 16:30	**A chimeric bi-specific neutralizing antibody for HIV prevention and immunotherapy** Prof Z Chen
16:30 – 18:00	**Macrophages - cells found in all tissues that contribute to development, homeostasis, repair and disease** Prof J Pollard
18:00 – 18:15	**Course Closing Address** Prof CS Lau and Prof T Mak
19:00 – 21:00	**Closing Dinner for all speakers and participants** Venue: The Hong Kong Academy of Medicine, 99 Wong Chuk Hang Road, Hong Kong (Tel: 2871 8787)

Abstract

A Prodrug of EGCG Suppresses Endometrial Cancer and Angiogenesis via Regulating Tumor-Associated Macrophages

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Endometrial cancer is a common gynecological cancer that arises from the endometrium, with increasing incidents in Asian countries. Within the endometrial tumor microenvironment is a complex system composed of many cell types, including endothelial cells and macrophages. Although under certain circumstances macrophages can kill the tumor cells, they can also act as tumor promoters by secreting a variety of factors that directly stimulate tumor growth, metastasis and angiogenesis. These are known as tumor-associated macrophages (TAMs). Hence, we speculated that specifically targeting TAMs or reprogramming them might be an approach for treating for endometrial cancer.

(−)-Epigallocatechin-3-gallate (EGCG), the major polyphenol in green tea, has been is associated with anti-cancer benefits. However, EGCG is notably unstable and is known to have poor bioavailability. We therefore produced a synthetic derivative of EGCG (ProEGCG) with enhanced stability and improved bioavailability. Previous studies have demonstrated the inhibitory capability of ProEGCG on the development, growth and angiogenesis of experimental endometriosis in mice and breast carcinoma in vitro. These data indicated that ProEGCG may serve as a novel potent anticancer agent of broad clinical value. However, it remains unknown whether ProEGCG could inhibit endometrial cancer by targeting TAMs.

In the present study, we evaluated the effects of ProEGCG on TAMs, in combination with its antitumor effects. To elucidate the antitumor effect of ProEGCG on endometrial cancer and angiogenesis, subcutaneous xenografts were established by inoculating RL95-2 cells and treated with oral vehicle (olive oil) and ProEGCG respectively. 35 days later, tumor growth was significantly inhibited by ProEGCG. Mouse CD34 staining of tumor lesions showed that ProEGCG could reduce microvessel density, which indicated its anti-angiogenesis. mRNA microarray of tumor lesions indicated that CCL2 and VEGFA were down-regulated by ProEGCG. IHC staining showed that infiltration of TAMs stained by CD163 and F4/80 antibodies was inhibited and VEGF expression was also down-regulated in ProEGCG group.

Our study is the first to reveal a novel mechanism of the anti-tumor effect of ProEGCG which inhibited angiogenesis by targeting TAMs. Moreover, these findings provided that ProEGCG would be a promising drug for clinical treatment of endometrial cancer.

Abstract

A study of MDSC mediated immunosuppression in endometriosis

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Endometriosis is a chronic disorder characterized by presence of endometrium outside the uterine cavity. In healthy women, the ectopic endometrial cells are normally eliminated by physiological immune surveillance. In women with endometriosis, the immune cells are not able to eradicate the ectopic endometrial cells, but facilitate and promote their survival and growth. The endometrium immune escape mediated by abnormal suppressive activities of the immune cells has been reported but the underlying mechanism are not well defined yet.

Myeloid-derived suppressor cells (MDSCs) are a population of suppressive cells negatively regulate immune responses in cancer and other diseases, but MSDCs in endometriosis have not been studied before. Here we find that mouse $CD11b^{+}Gr1^{+}$ and human HLA-DR^{-} $CD11b^{+}CD33^{+}$ MDSCs are increased in our experimental endometriosis model in mice and endometriosis patients. Notably the evaluated mouse endometriosis $CD11b^{+}Gr1^{+}$ MDSCs also exhibit suppressive T cell response, arginase activity, reactive oxygen species production. In contrast, the mouse endometriosis MDSCs mainly expand transiently in peritoneum, but not in bone marrow and spleen; and present with distinct chemotaxic profiles, including IL1β/2Rα/3/4/6 cytokines and CXCL1/2 chemokines. Further we demonstrate that depletion of the mouse endometriosis $CD11b^{+}Gr1^{+}$ MDSCs by anti-Gr1 antibody inhibit the growth and development of the endometriotic lesions in mice. Given that MDSCs contribute to negative regulation of immune responses and promote progression of cancer and other pathological conditions via STATs signalling. Based on our findings, we proposed endometriosis MDSCs negatively regulate the immune responses and promote the growth and development of endometriosis; and the underlying mechanism involves IL1β/2Rα/3/4/6- and CXCL1/2-mediate induction of STATs, in turn suppress the immune surveillance in endometriosis.

Endometriosis is a common gynaecological disorder mainly involve locally in peritoneal cavity with unclear immunological pathophysiology and modulation. Studying the endometriosis MDSCs will shed lights to understand the underlying mechanism of the endometrium immune escape in the development of the endometriosis. In long run, our study may also develop the endometriosis MDSC subsets and associated chemotaxic molecules as potential diagnostic marker for prediction and prognosis of the condition and possible therapeutic target for the treatment of endometriosis.