論文の内容の要旨

獣医学専攻

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論文題目　Investigation of the role of prostaglandin D_2 in tumor microenvironment

（腫瘍微小環境におけるプロスタグランジン D_2 の役割解明）

Background and Aim

Tumor microenvironment, which is composed of non-tumor cells such as ECs and immune cells, has a key role in tumor growth and metastasis. Tumor cells manipulate this microenvironment to acquire adequate nutrients/oxygen and also avoid host immunosurveillance.

PGD_2 is one of major PGs that is synthesized by COX and L- or H-PGDS, and produced PGD_2 exerts its bioactivity through two receptors, DP and CRTH2. PGD_2 has been known to regulate physiological sleep, allodynia response, and some allergic diseases. Besides, our group recently reported the anti-inflammatory role of H-PGDS-derived PGD_2 in dermatitis, rheumatoid arthritis, acute lung injury, food allergy, pulmonary fibrosis, and anaphylaxis. We also found that mast cell H-PGDS-derived PGD_2 inhibited the growth of mice LLC by attenuating tumor vascular permeability and angiogenesis. However, there are still uncertain whether L-PGDS-derived PGD_2 regulates tumor growth and PGD_2 affects tumor metastasis.

Results

In comprehensive analysis of mice melanoma ECs, I found marked increase in mRNA expression of L-PGDS compared to the normal ECs. Immunostaining of mice melanoma revealed protein expression of L-PGDS in the ECs. *In situ* hybridization also showed mRNA expression of L-PGDS in the ECs of human melanoma and oral squamous cell carcinoma. *In vitro* experiments showed that stimulation with tumor cell-derived IL-1 and TNF-α increased mRNA expression of L-PGDS and production of PGD_2 in the human normal ECs. I also investigated the contribution of L-PGDS-PGD_2 to tumor growth and vascularization. Systemic or EC-specific deficiency of L-PGDS accelerated the growth of melanoma in mice, while the treatment with a PGD_2 receptor DP agonist attenuated it. Morphological and *in vivo* studies showed that endothelial L-PGDS deficiency showed functional changes of tumor ECs such as accelerated vascular hyper-permeability, angiogenesis, and EndMT in tumors, which in turn reduced tumor cell apoptosis.

Conclusion

In tumor growth, endothelial L-PGDS-derived PGD_2 attenuated the growth of mice melanoma through inhibition of tumor vascular permeability, angiogenesis, and EndMT. This study provides a significant insight on tumor microenvironment and might lead to a novel therapeutic strategy against tumor growth and metastasis.