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Immune Cell Responses in Gastric Carcinoma: An Analysis Based on Histopathology

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1. Introduction

Recent advances in tumor immunology have established the concept of tumor immunosurveillance, and cancers are considered to have developed after overcoming these host immunosurveillance mechanisms. As a result, established cancers are in an immunosuppressive microenvironment (Dunn et al. 2004; Finn 2008).

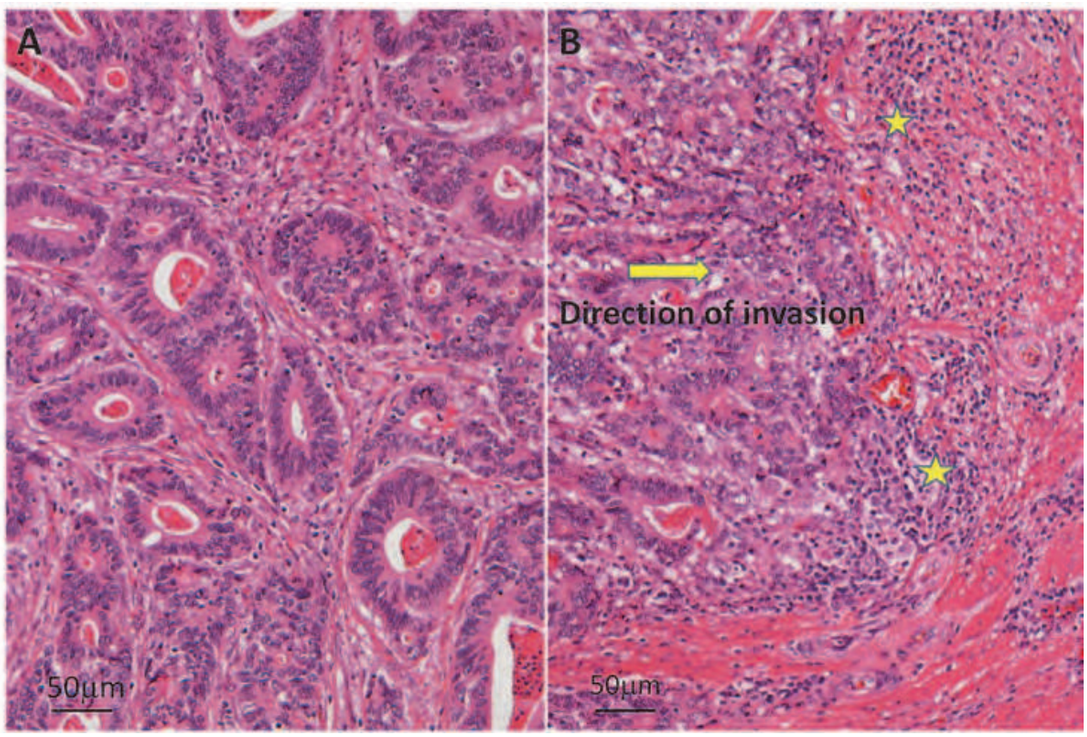

Fig. 1. Histology of conventional gastric cancer. **A)** Area inside conventional gastric cancer (well differentiated tubular adenocarcinoma). The stromal area is infiltrated by scanty tumor-infiltrating lymphocytes, a basic feature of cancer. **B)** Area of invasive margin in the same case. Note the presence of tumor-infiltrating lymphocytes along the invasive margin (asterisks). An arrow indicates the direction of invasion.

This concept implies that established tumors are either devoid of immune cell infiltrate (Fig. 1A) or, if present, the immune cell infiltrate is suppressed. Routine histopathological examination reveals that human cancer tissues are infiltrated to varying degrees by tumor-infiltrating lymphocytes, which if present, usually accumulate along the invasive margin (tumor-host interface) (Fig. 1B). In contrast, the stroma inside tumors tends to be devoid of tumor-infiltrating lymphocytes (Fig. 1A). Unraveling the biological significance of tumor-infiltrating lymphocytes is not straightforward because of the complexity of the cellular compositions of tumor-infiltrating lymphocytes themselves (Yu and Fu 2006). In several cancers, it is known that higher levels of tumor-infiltrating lymphocytes are prognostic of longer survival rates in patients (Naito et al. 1998; Sato et al. 2005; Galon et al. 2006; Sharma et al. 2007). Thus it appears likely that tumor-infiltrating lymphocytes may possess anti-tumor activity that alleviates cancer aggressiveness.

2. Gastric cancers with lymphoid stroma

Cancers with prominent tumor-infiltrating lymphocytic responses exist as extreme variants in tumor pathology; medullary carcinoma of the breast and nasopharyngeal carcinoma ("lymphoepithelial carcinoma") are two such examples. In gastric cancer, such variants are designated "gastric cancers with lymphoid stroma" or "lymphoepithelioma-like cancer".Such cancers are characterized by poorly differentiated cancer cells with a syncytial

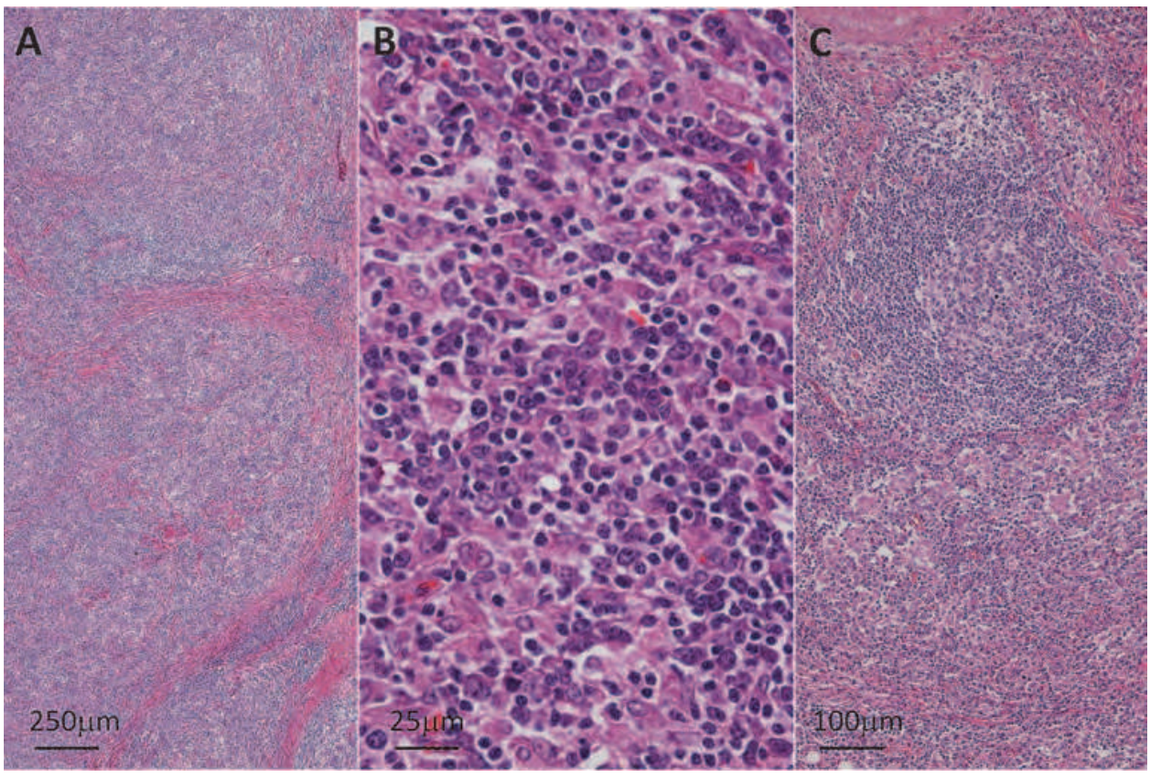

Fig. 2. A-C. **A, B**) Histology of lymphocyte-rich gastric cancer (typical case of lymphoepithelioma-like cancer). Low (A) and high power magnification (B). Note massive infiltration by lymphocytes, and poorly differentiated cancer cells. **C**) Occasionally formed lymph follicle with a germinal center.

appearance and massive lymphoid infiltrate (Fig. 2A, B). Formation of lymph follicles containing a germinal center is usually observed (Fig. 2C). The prognosis for typical cases is better than that for conventional gastric cancer cases (Watanabe et al. 1976; Minamoto et al. 1990). This suggests that the lymphoid stroma may produce an antitumor immune response. Most gastric cancers with lymphoid stroma are associated with Epstein-Barr virus (EB virus) (Tokunaga et al. 1993; Fukayama et al. 2010). It should be noted, however, that not all Epstein-Barr virus-associated gastric cancers have lymphoid stroma. In this chapter, attention is focused on how lymphoid infiltrate occurs in gastric cancers.

3. Cellular composition of the lymphocyte-rich stroma

The term "lymphocyte-rich gastric cancers" used here includes typical gastric cancers with lymphoid stroma (Fig. 2 A-C) and other types of gastric cancers associated with tumor-infiltrating lymphocytic responses in nearly whole stroma. The lymphocyte-rich gastric cancers are consistently infiltrated by $CD3^+$ T cells (Fig. 3A), among which both $CD8^+$ and $CD4^+$ T cells are present. Key antigen presenting cells, the $CD83^+$ myeloid-derived dendritic cells (Heath and Carbone 2009) are also distributed in the T cell-rich stroma of the lymphocyte-rich gastric cancers (Fig. 3B). B-lymphocytes are not generally abundant in the tissue (Fig. 3C), except in areas containing lymphoid follicles where abundant B-cell populations are observed. Saiki et al.'s (1996) finding that approximately 13% of $CD8^+$ T cells exhibited Ki-67 immunoreactivity implies that active immune responses with lymphocyte proliferative activity take place in lymphocyte-rich gastric cancers.

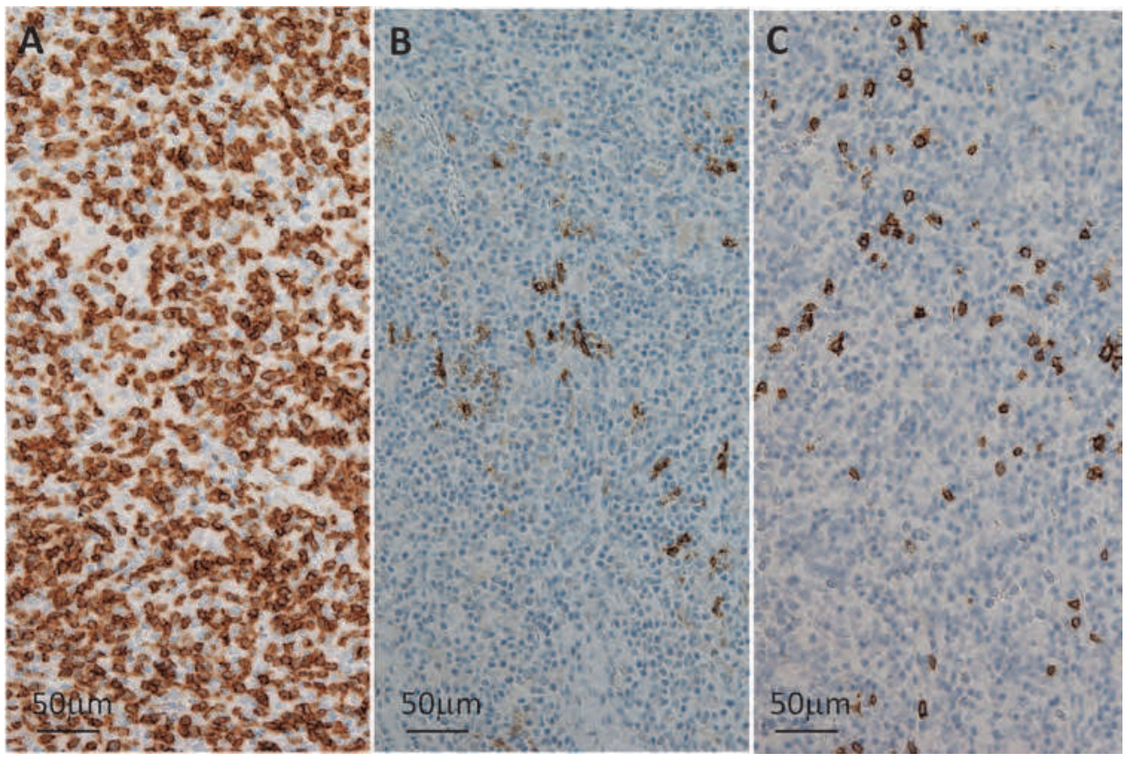

Fig. 3. Single immunohistochemistry of lymphocyte-rich gastric cancers for CD3 (**A**), CD83 (**B**), and CD20 (**C**) (signals shown with brown, hematoxylin-nuclear counterstaining). Note abundance of T-lymphocytes with mature dendritic cells. B-lymphocytes are not abundant.

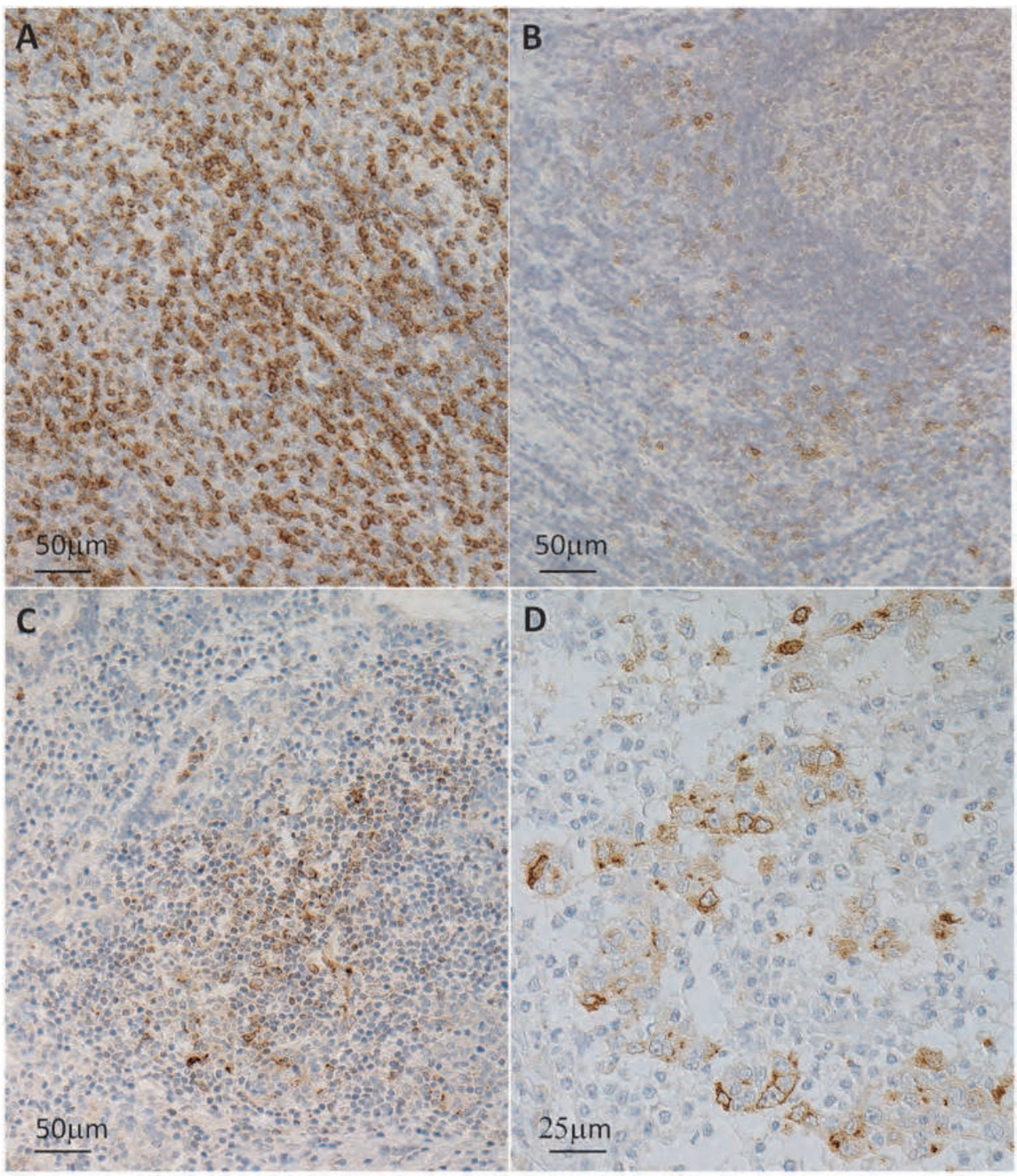

Fig. 4. A-D. Single immunohistochemistry of lymphocyte-rich gastric cancers for CXCR3 (**A**), CCR4 (**B**), and CXCL9 (**C** and **D**) (signals shown with brown, hematoxylin-nuclear counterstaining). **A**) Note abundance of CXCR3-positive lymphocytes. **B**) Expression of chemokine receptor CCR4 is sparse, which is mainly expressed by Th2 cell and regulatory T cells **C**) CXCL9 is mainly localized in stromal cells in lymphocyte-rich stroma. **D**) Only a part of cancer cells expresses CXCL9.

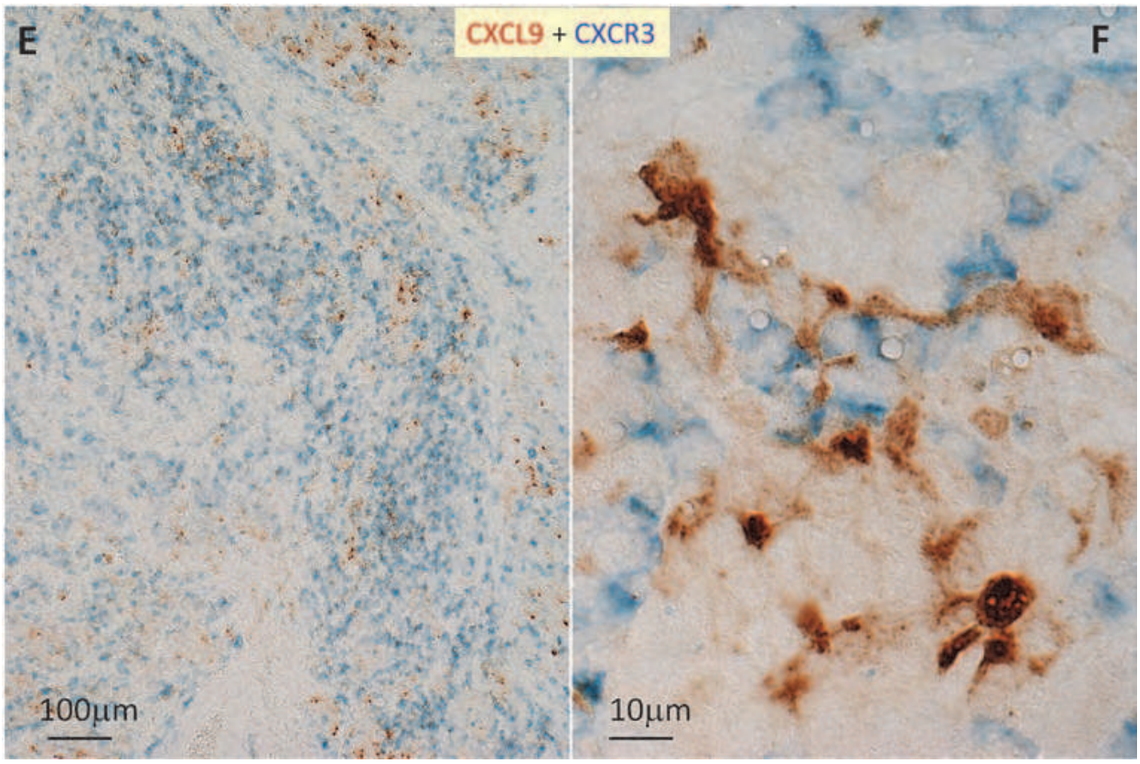

Fig. 4. E, F. Double staining of lymphocyte-rich gastric cancer for CXCL9 (brown) and CXCR3 (blue). Low power (**E**) and high power magnification (**F**) reveals that CXCL3$^+$ stromal cells are in close contact with CXCR3$^+$ lymphocytes; this is reminiscent of a dendritic cell-T cell distribution in the secondary lymphoid tissues such as lymph nodes.

4. Expression of chemokine CXCL9 and receptor CXCR3 in lymphocyte-rich gastric cancers

Chemokines are chemotactic cytokines, which cause migration of leukocytes and other cells that express cognate chemokine receptors (Zlotnik and Yoshie 2000; Murphy et al. 2000; Allen et al. 2007). Chemokines and their receptors play important roles in inflammation, lymphoid organogenesis and cancer cell invasion and/or metastasis. The chemokine receptor CXCR3 and two of its cognate ligands, CXCL9 (MIG) and CXCL10 (IP10) are described here because CXCR3 is widely expressed by T helper type 1 (Th1) cells and CD8$^+$ T cells (Zlotnik and Yoshie, 2000; Ohtani et al. 2009).

By immunohistochemistry, CXCR3$^+$ lymphocytes are abundant in the lymphoid stroma of lymphocyte-rich gastric cancers (Fig. 4A), which contrasts markedly with the sparse distribution of CCR4$^+$ cells (Fig. 4B). This suggests a predominance of Th1 cells over Th2 cells in this tissue. CXCR3$^+$ cells are sparse in the lymphoid follicles (B-cell zone). The CXCR3-ligands, CXCL9 and CXCL10, are mainly expressed by dendritic-shaped "stromal cells" that were distributed in CXCR3$^+$ cell-rich lymphoid stroma (Fig. 4C). CXCL9 and CXCL10 are also expressed in only a small portion of cancer cells (Fig. 4D). Of the two, CXCL9 is more frequently observed in stromal cells of lymphocyte-rich gastric cancers than CXCL10. The author has designated this type of distribution "CXCR3$^+$ T cell-CXCL9$^+$ stromal cell clustering", which is clearly observed by double staining (Fig. 4E) (Ohtani et al.

2009, 2010). At higher magnification, a close cell-to-cell contact between CXCL9+ stromal cells and CXCR3+ cells is revealed (Fig. 2F). This clustering, reminiscent of T cell-dendritic cell clustering in the secondary lymphoid tissues, is confined to lymphocyte-rich gastric cancers, but not conventional gastric cancers. Hence, the results thus far suggest that the Th1 response is dominant and that CXCL9+ stromal cells are important for large-scale infiltration by CXCR3+ T cells.

5. Cell identification of CXCL9+ stromal cells

The shape of CXCL9+ stromal cells suggests that they may be dendritic cells. CD83+ mature, myeloid-derived dendritic cells are in fact found to be distributed in lymphocyte-rich gastric cancers (Fig. 3B). However, double immunohistochemistry reveals that only 10-20% of CXCL9+ stromal cells co-express CD83 (Fig. 5A), and half of CXCL9+ stromal cells co-expresses fascin (a wide marker of dendritic cells) (Fig. 5B). DC-Lamp, another marker of mature dendritic cells, is expressed also in a part of CXCL9+ stromal cells (Fig. 5C). A half of CXCL9+ stromal cells expresses CD68, a marker of macrophages including immature dendritic cells.

These data suggest that only a minor part of CXCL9+ stromal cell populations comprises mature, myeloid-derived dendritic cells, but more than half are stromal cells (probably myeloid-derived cells) that cannot be classified precisely at present.

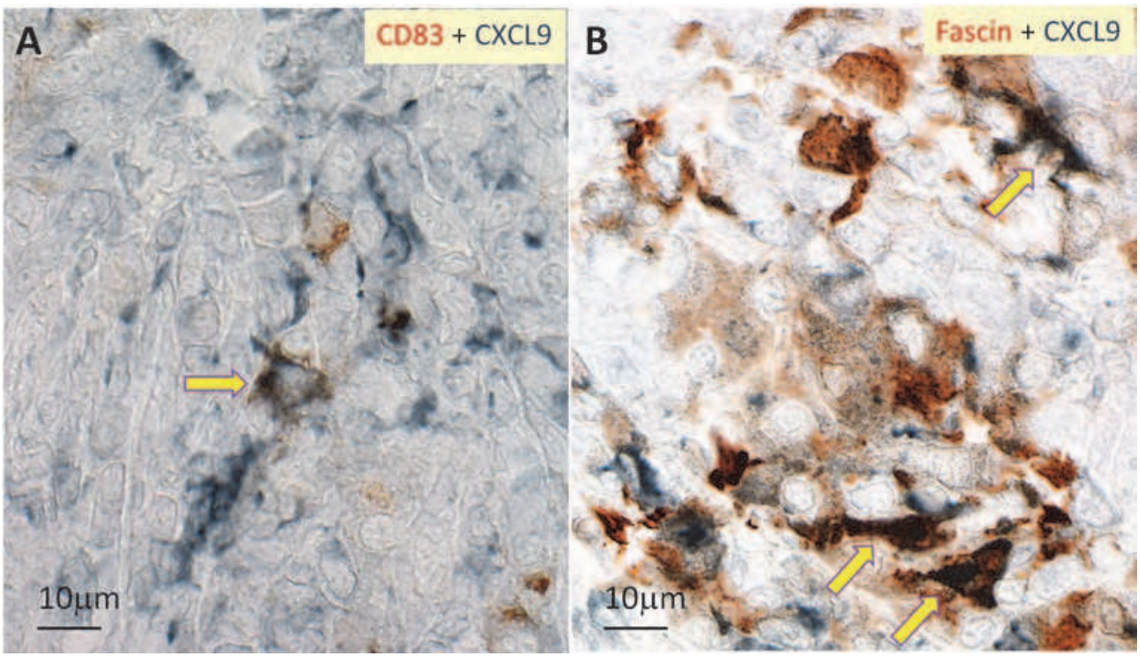

Fig. 5. A and B. **A)** Double staining for CD83 and CXCL9. An arrow indicates CD83+ (brown) mature dendritic cells also expressing CXCL9 (blue). **B)** Double staining for fascin (brown) and CXCL9 (blue). Arrows indicate fascin+ dendritic cells co-expressing CXCL9. These data suggest that a part of CXCL9-positive stromal cells are dendritic cells.

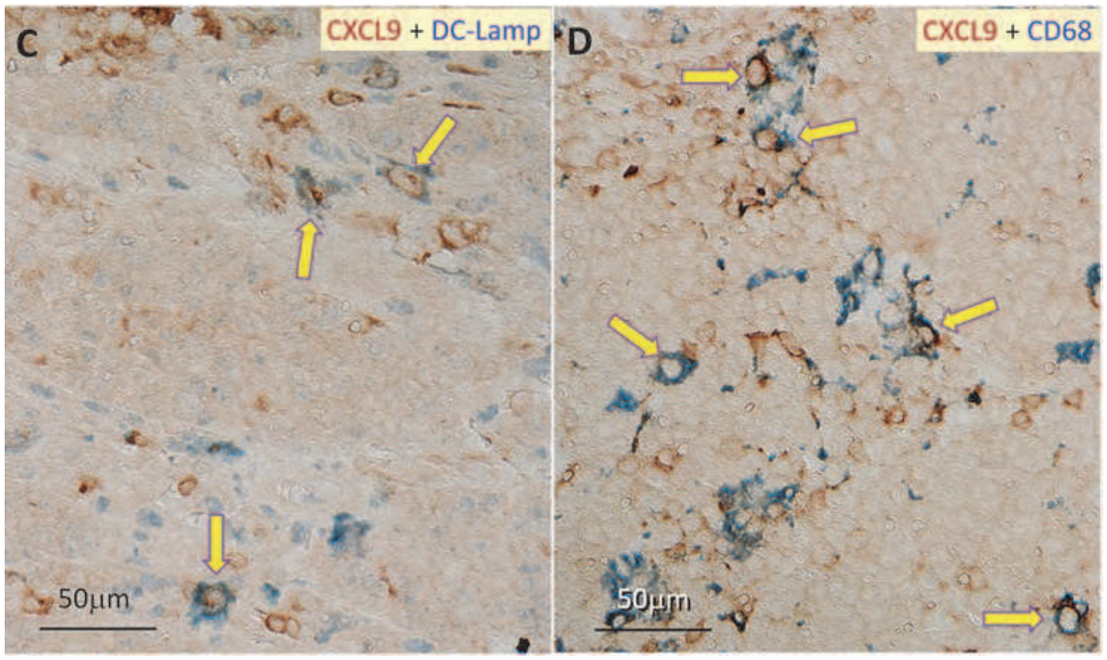

Fig. 5. C and D. **C**) Double staining for CXCL9 and DC-lamp (using frozen section). Arrows indicateDC-Lamp$^+$ mature dendritic cells (blue) also expressing CXCL9 (brown) Double staining for CXCL9 (brown) and CD68 (blue). Arrows indicate double positive cells. These cells may be macrophages or immature dendritic cells.

6. Proliferative activity of T cells in close contact with CXCL9$^+$ stromal cells

The proliferative activity of T cells in the histopathological samples can be assessed using Ki-67 immunohistochemistry. As shown in Fig. 6A, double staining reveals that CD45RO$^+$ T cells (red) and CXCL9$^+$ stromal cells (dark blue) exhibit close cell-to-cell contact (similar to Fig. 2B). Fig. 6B has Ki-67 immunostaining (brown) added to the double staining. This triple staining shows that CD45RO$^+$(red)Ki-67$^+$(brown) cells exist in close contact to CXCL9$^+$ stromal cells (dark blue) (Fig. 6B, arrows). Approximately 10% of CD45RO$^+$ cells co-express Ki-67. This indicates that CD45RO$^+$ T cells in close contact with CXCL9$^+$ stromal cells have proliferative activity. Taking account of the well-characterized T-cell and dendritic cell interactions, the data here imply that when CXCR3$^+$ T cells are in close contact with CXCL9$^+$ stromal cells, they may receive proliferative stimuli. Therefore, the lymphoid stroma is not a mere aggregation of lymphocytes, but a place where significant T cell–stromal cell interactions can occur.

7. Similarity to the regional lymph nodes

Given that peripheral tissue (with inflammatory changes) has a close connection with regional lymph nodes, it is important to compare potential changes occurring between gastric cancers and regional lymph nodes. As shown in figure 7A, CXCL9$^+$ stromal cells are abundantly distributed in the T-cell zone in the regional lymph nodes of lymphocyte-rich gastric cancers. In contrast, regional lymph nodes in conventional gastric cancers show only sporadic expression of CXCL9$^+$ cells (Fig. 7B). Hence, histopathological identification of CXCL9$^+$ cells in both primary tumor and regional lymph nodes suggests that a functional relationship exists between them.

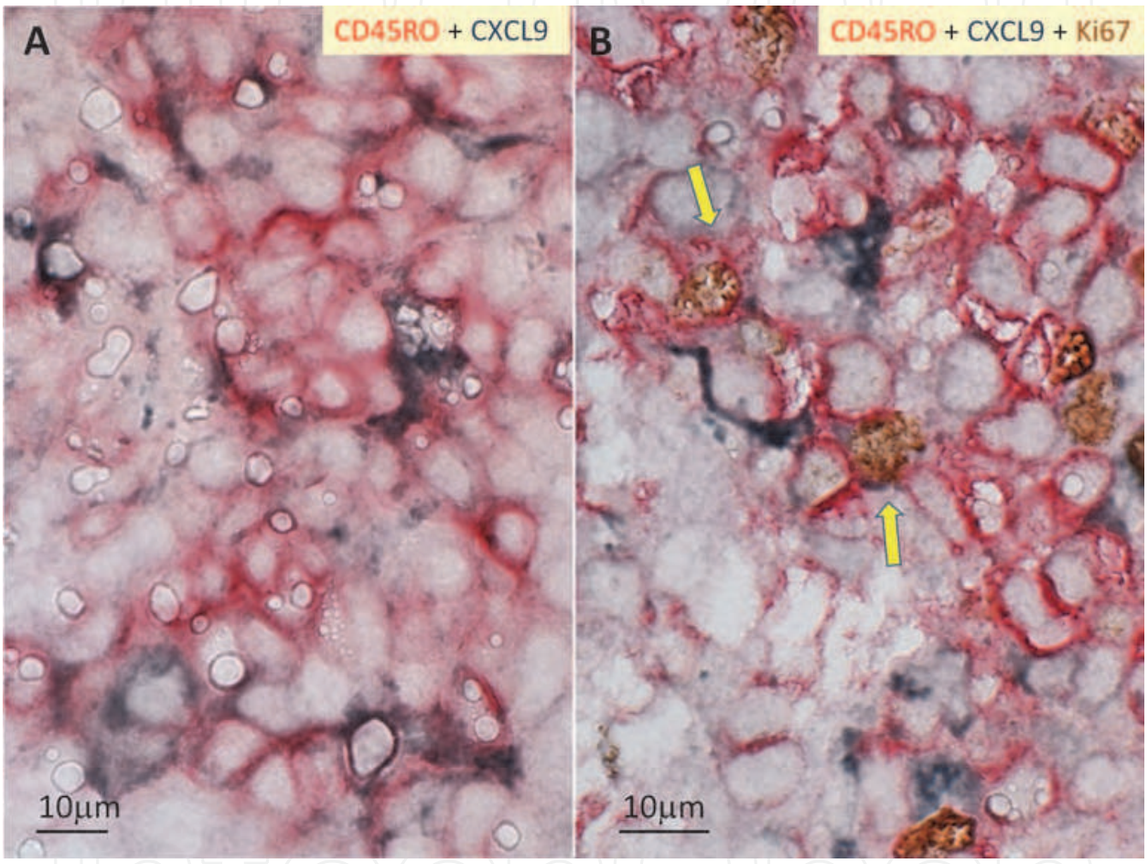

Fig. 6. Immunohistochemical analyses for proliferative activity of T cells in lymphocyte-rich gastric cancer. **A**) Double staining for CD45RO (red) and CXCL9 (dark blue), revealing that $CXCL9^+$ stromal cells are in close contact with $CD45RO^+$ T cells (similar to the results shown in Fig. 2B). **B)** Triple staining for CD45RO (red) + CXCL9 (dark blue) + Ki-67 (brown). Arrows indicate $Ki\text{-}67^+$ T cells (brown and red) that are in close contact with $CXCL9^+$ stromal cells (dark blue). This suggests that T cells in close contact with $CXCL9^+$ cells are proliferating in lymphocyte-rich gastric cancers.

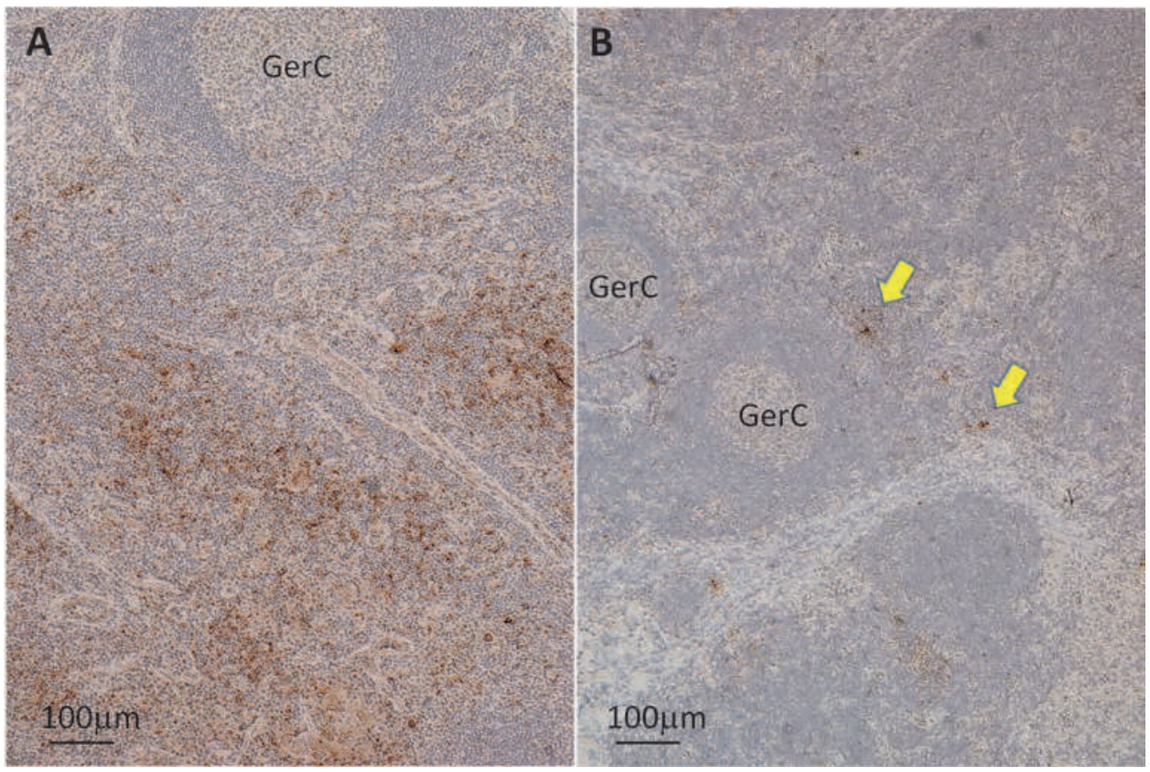

Fig. 7. Immunohistochemistry for CXCL9 in regional lymph nodes in lymphocyte-rich- (**A**) and conventional (**B**) gastric cancers. Note the abundance of CXCL9$^+$ stromal cells in regional lymph nodes in lymphocyte-rich gastric cancers (A), contrasted by sparse distribution of CXCL9$^+$ stromal cells (arrows) in regional lymph node of conventional gastric cancer (B). GerC in (B) and (C) represents germinal centers.

8. Regulatory T cells

The data thus far suggests the presence of pro-immune responses in lymphocyte-rich gastric cancers. However, current opinion on tumor immune evasion mechanisms maintains that immunosuppressive factors play a major role. Regulatory T-cells are one type of cell that exerts a suppressive function, and forkhead box protein-3 (Foxp3) is a reliable marker of the cells (Zou 2006). In gastric cancer, diffuse distribution of regulatory T cells is associated with a poorer prognosis of patients (Mizukami et al. 2008a,b). Fig. 8A shows the distribution of Foxp3$^+$ regulatory T-cell in lymphocyte-rich gastric cancer. Using Foxp3 as a marker, quantitative immunohistochemistry shows a small increase in the number of regulatory T-cells in lymphocyte-rich gastric cancers, compared with conventional gastric cancers (Fig. 8B). This sharply contrasts with a marked increase in CXCR3$^+$ lymphocytes observed in lymphocyte-rich gastric cancers compared with conventional gastric cancers (Fig. 8C). Hence, the ratio of CXCR3$^+$ lymphocytes/regulatory T-cells is higher in lymphocyte-rich gastric cancers than in conventional gastric cancers. Overall, this suggests that the lymphoid stroma in lymphocyte-rich gastric cancers is shifted towards a pro-immune status compared with conventional gastric cancers. And, it is clear that immunosuppressive aspects of lymphoid stroma cannot be explained by a mere increase in regulatory T-cells alone.

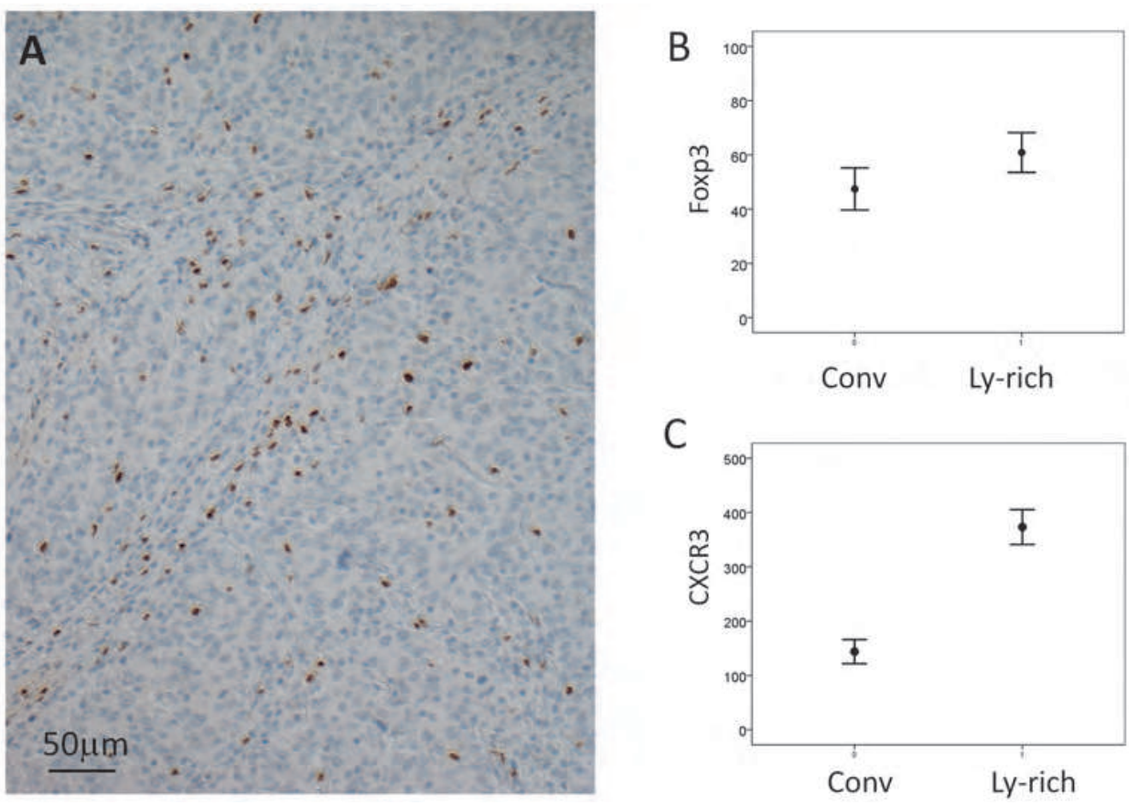

Fig. 8. Analysis on regulatory T cells. **A**) Immunohistochemitry for Foxp3 reveals that regulatory T-cells are also distributed in lymphocyte-rich gastric cancer. **B**) However, regulatory T-cells are mildly elevated in lymphocyte-rich gastric cancers than in conventional gastric cancer. (**C**) There are a sharp increase in the number of $CXCR3^+$ cells in lymphocyte-rich gastric cancers as compared with conventional gastric cancer (error bars for panels B and C are the mean ± standard error). Methods of B) and C). Immunohistochemistry for Foxp3 was performed on routine histopathological slides. The numbers of $Foxp3^+$ cells per unit area (0.0625 mm^2) were counted manually suing a 40x objective lens. At least three areas were counted. In lymphocyte-rich gastric cancer, areas with average infiltration were counted. In conventional gastric cancers, the most densely infiltrated areas were counted. Conv, conventional gastric cancer. Ly-rich, lymphocyter-rich gastric cancer. Verticals bar in B) and C) represent number of cells per unit area (0.0625 mm^2).

Next the immunohistochemical distribution of chemokine CCL22 (MDC) is described. CCL22 is one of the cognate ligands of CCR4 which is frequently expressed by regulatory T-cells and Th2 cells. CCL22 is focally expressed by mature dendritic cells in lymphocyte-rich gastric cancers, but not in conventional gastric cancers (Ohtani et al. 2010). It is generally believed that tumor-derived CCL22 promotes accumulation of $CCR4^+$ regulatory T-cells, which subverts immune responses in cancer (Menetrier-Caux et al. 2009). Tan et al. (2011) suggested that regulatory T-cells can promote tumor metastasis through RANKL, a mechanism distinct from an immunoregulatory one. Therefore, it is conceivable that dendritic cells in lymphocyte-rich gastric cancers may have both tumor-inhibitory and tumor-promoting properties

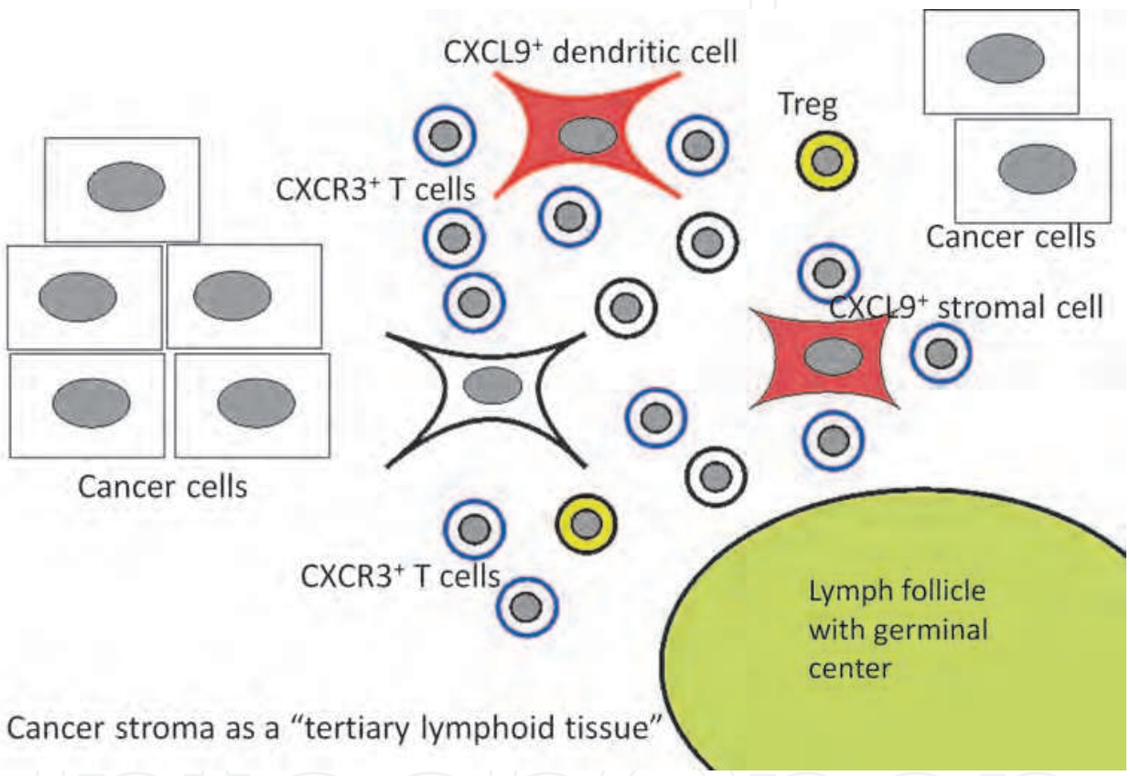

Fig. 9. Schematic summary of the results. Lymphocyte-rich gastric cancers are characterized by an abundance of $CXCR3^+$ T cells with $CXCL9^+$ stromal cells ($CXCR3^+$ T cell-$CXCL9^+$ stromal cell clustering). Dendritic cells are also distributed in the section. Together with the formation of lymphoid follicles with germinal centers, these data suggest that the stroma of lymphocyte-rich gastric cancer is a tertiary lymphoid tissue.

9. Conclusions

Fig. 9 is a schematic summary of this chapter. This depicts stromal elements of lymphocyte-rich gastric cancers. T cells are predominant in this lymphoid stroma, where chemokine CXCL9 and chemokine receptor CXCR3 are expressed by stromal cells and T cells, respectively, to form $CXCL9^+$ stromal cell-$CXCR3^+$ T cell clustering. Mature, myeloid-derived dendritic cells are also distributed in the tissue. A part of $CXCL9^+$ cells corresponds to these mature dendritic cells. However, a large part of $CXCL9^+$ stromal cells remains unclassified.

Regulatory T-cells are also present, but their relative density is lower in lymphocyte-rich gastric cancers than in conventional gastric cancers. Together with the occasional formation of lymph follicles with a germinal center, the lymphoid stroma in lymphocyte-rich gastric cancer is judged to be similar to the secondary lymphoid tissue (i.e., lymph nodes or Peyer patches). Lymphoid tissues newly formed in the peripheral tissues during chronic inflammation are designated "tertiary lymphoid tissues" (Aloisi et al. 2006). The author proposes, therefore, that lymphoid stroma in lymphocyte-rich gastric cancer can be regarded as tertiary lymphoid tissue (Ohtani et al. 2009). Hence, immunostimulatory aspects of lymphocyte-rich gastric cancers have been clarified in this chapter. A mere increase of regulatory T-cells is not observed in lymphocyte-rich gastric cancer. Further analyses of the immunoregulatory aspects of lymphoid stroma are now required because immunosubversion is considered to be a major obstacle to successful immunotherapy of cancer.

10. Acknowledgments

The author is grateful to Drs. Osamu Yoshie, Masaaki Miyazawa, Takashi Nakayama, Fuminori Katou, Eiichi Sato, Noriko Kimura, Hiroshi Naganuma, and Yuriko Saiki for their cooperation. Clerical assistance by Ms. Fumiko Date is also greatly appreciated.

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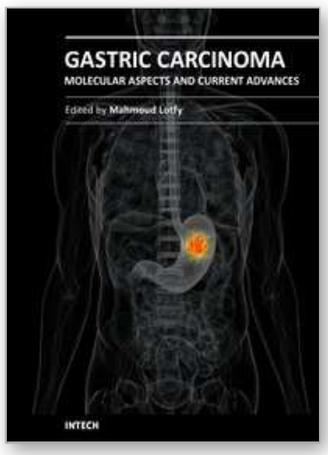

Gastric Carcinoma - Molecular Aspects and Current Advances
Edited by Prof. Mahmoud Lotfy

ISBN 978-953-307-412-2
Hard cover, 354 pages
Publisher InTech
Published online 15, June, 2011
Published in print edition June, 2011

Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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