International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Evaluation of Tumor Associated Macrophages and Vascular Endothelial Growth Factor Receptor expression in Colorectal Carcinoma: An Immunohistochemical Correlation Study

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Abstract: ***Colorectal cancer (CRC) is one of the most common malignancies worldwide and its progression is influenced by the tumor microenvironment. Tumor-associated macrophages (TAMs), particularly the M2 phenotype, play a critical role in tumor progression, immune suppression and angiogenesis. Vascular endothelial growth factor receptor (VEGFR) signaling is a major driver of tumor angiogenesis. This study aimed to evaluate the correlation between tumor-associated macrophages and VEGFR expression in colorectal carcinoma using immunohistochemistry. A cross-sectional study was conducted on 52 cases of colorectal carcinoma received in the Department of Pathology, Osmania General Hospital, Hyderabad. Immunohistochemical staining was performed for CD163 to identify tumor-associated macrophages and VEGF to evaluate angiogenic activity. Expression levels were scored semi-quantitatively and correlated with clinicopathological parameters. Statistical analysis was performed using Spearman correlation and Chi-square tests. A strong positive correlation was observed between CD163 and VEGFR expression (Spearman $\rho = 0.659$, $p < 0.001$). Increased expression of both markers was also associated with advanced tumor stage and aggressive pathological features. The study demonstrates that tumor-associated macrophages are significantly associated with increased VEGFR expression, suggesting their role in promoting tumor angiogenesis in colorectal carcinoma.***

Keywords: Colorectal cancer, Tumor associated macrophages, CD163, VEGF, Angiogenesis, Immunohistochemistry

1. Introduction

Colorectal cancer is one of the leading causes of cancer-related morbidity and mortality worldwide. Tumor progression is influenced not only by malignant epithelial cells but also by the surrounding tumor microenvironment which includes immune cells, stromal cells and inflammatory mediators.

Tumor-associated macrophages represent a major component of the tumor microenvironment. Macrophages within tumors often acquire an M2-like phenotype that promotes tumor growth, immune suppression and angiogenesis. CD163 is widely used as an immunohistochemical marker for M2 macrophages.

Angiogenesis is a key process in tumor growth and metastasis. Vascular endothelial growth factor (VEGF) and its receptors play a pivotal role in the formation of new blood vessels that support tumor expansion.

Recent studies have suggested that TAMs contribute to tumor angiogenesis by secreting pro-angiogenic factors including VEGF. However, the relationship between TAM infiltration and VEGFR expression in colorectal carcinoma remains incompletely understood.

The present study was undertaken to evaluate the correlation between tumor-associated macrophages and VEGFR expression in colorectal carcinoma using immunohistochemistry

2. Literature Review

Several studies have highlighted the importance of tumor microenvironment in cancer progression. Tumor-associated macrophages are known to promote tumor growth, invasion and metastasis.

Mantovani et al. described the role of macrophages in cancer-related inflammation and tumor progression. TAMs produce multiple cytokines and growth factors that stimulate angiogenesis and tumor proliferation.

Studies on colorectal carcinoma have demonstrated that increased macrophage infiltration correlates with advanced tumor stage and poor prognosis. CD163-positive macrophages have been reported to be associated with enhanced tumor angiogenesis.

VEGF signaling plays a key role in tumor vascularization. VEGF binding to its receptors stimulates endothelial cell proliferation and formation of new blood vessels that support tumor growth.

The interaction between TAMs and VEGF signaling pathways suggests that macrophages may enhance tumor angiogenesis. Therefore, evaluating the relationship between TAM density and VEGFR expression may provide valuable insights into tumor biology.

3. Materials and Methods

This study was conducted in the **Department of Pathology, Osmania Medical College and Osmania General Hospital, Hyderabad**.

Study Design
Cross-sectional observational study.

Study Period
2023–2026

Sample Size
52 cases of histopathologically confirmed colorectal carcinoma.

Inclusion Criteria
- Histologically confirmed colorectal carcinoma
- Adequate tissue for immunohistochemistry

Exclusion Criteria
- Inadequate tissue samples
- Previously treated tumors

Immunohistochemistry
Immunohistochemical staining was performed on formalin-fixed paraffin-embedded tissue sections using:
- **CD163 antibody** – marker for tumor associated macrophages
- **VEGF antibody** – marker for angiogenesis

Scoring Method
Staining intensity and proportion of positive cells were assessed semi-quantitatively. Scores were categorized as low or high expression.

Statistical Analysis
Statistical analysis was performed using:
- Spearman correlation test
- Chi-square test

A **p-value <0.05** was considered statistically significant.

4. Results

A total of **52 cases of colorectal carcinoma** were included in the study.

The majority of cases demonstrated variable expression of both CD163 and VEGF markers.

Spearman correlation analysis demonstrated a significant positive correlation between CD163 expression and VEGFR expression ($\rho \approx 0.65$, $p < 0.001$).

Table 1: CD163 Expression
CD163 immunostaining highlighted macrophages present in the tumor stroma. Increased macrophage infiltration was observed in several cases.

CD163 Expression	Number of cases	%
Low expressiom	26	50
High expression	26	50
Total	52	100

Table 2: VEGF Expression
VEGF expression was observed in tumor cells and endothelial cells indicating angiogenic activity.

VEGF Expression	Number of cases	%
Low expressiom	24	46.2
High expression	28	53.8
Total	52	100

Table 3: Correlation Between CD163 Expression and VEGFR Expression

CD163 Expression	VEGF Low	VEGF High	Total
CD163 Low	18	8	26
CD163 High	6	20	26
Total	24	28	52

Statistical Test: Spearman Correlation
Correlation coefficient (ρ) ≈ 0.65
p-value < 0.001 (statistically significant)

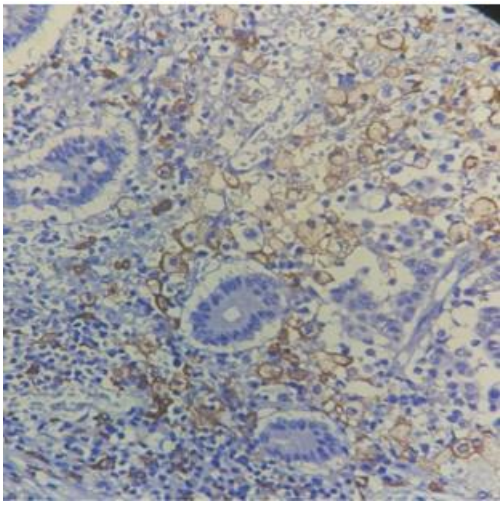

Figure 1: CD163 immunohistochemical staining showing tumor-associated macrophages in the tumor stroma of colorectal carcinoma (400× magnification).

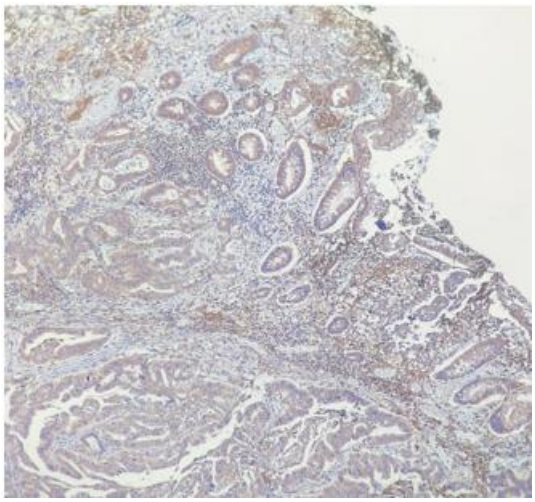

Figure 2: VEGF immunohistochemical staining demonstrating cytoplasmic positivity in tumor cells indicating angiogenic activity (400× magnification)

Correlation Analysis

Statistical analysis revealed a **positive correlation between CD163 expression and VEGFR expression**. Tumors with high macrophage infiltration showed increased VEGFR expression. This suggests that tumor-associated macrophages may contribute to angiogenesis in colorectal carcinoma.

5. Discussion

Tumor progression is strongly influenced by the tumor microenvironment. Among immune cells present within tumors, macrophages play a crucial role in regulating tumor growth and angiogenesis.

Tumor-associated macrophages typically exhibit an M2 phenotype which promotes tumor progression by releasing pro-angiogenic cytokines and growth factors. CD163 is considered a reliable marker for identifying these macrophages.

In the present study, increased CD163 expression was associated with increased VEGFR expression. This finding suggests that macrophage infiltration may enhance angiogenic signaling pathways within the tumor microenvironment.

Macrophages are known to secrete VEGF, transforming growth factor-β and other angiogenic mediators that stimulate endothelial cell proliferation and blood vessel formation. Increased angiogenesis facilitates tumor growth and metastasis.

Previous studies have reported similar findings where increased TAM density correlated with higher VEGF expression and aggressive tumor behavior.

The results of this study support the concept that tumor-associated macrophages contribute to tumor angiogenesis in colorectal carcinoma.

6. Study Limitations

The present study was limited by relatively small sample size and lack of long-term follow-up data. Larger multicenter studies are required to confirm the prognostic significance of tumor-associated macrophages and VEGFR expression in colorectal carcinoma

7. Conclusion

The present study demonstrates a significant correlation between tumor-associated macrophages and VEGFR expression in colorectal carcinoma.

Increased infiltration of CD163-positive macrophages is associated with increased angiogenic activity. These findings suggest that TAMs play an important role in tumor progression.

Evaluation of TAMs and VEGFR expression may serve as potential prognostic markers and therapeutic targets in colorectal carcinoma.

8. Future Scope

Further studies involving larger sample sizes and long-term follow-up are required to better understand the prognostic significance of tumor-associated macrophages and angiogenic markers in colorectal cancer.

Molecular studies evaluating additional angiogenic pathways may provide deeper insights into tumor microenvironment interactions.

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