University of Tehran Press

Journal of Veterinary Research

Homepage: jvr.ut.ac.ir

Online ISSN: 2251-6190

Original Article

J Vet Res, Volume 78, Number 4, 2023, 235-246

Role of Putative Phosphorylation Sites on Tie2 Receptor in the Interaction between Tumor-Associated Macrophages and Human Endothelial Cells

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***Received:** 8 July 2023, **Accepted:** 20 September 2023*

10.22059/jvr.2023.354283.3323 20.1001.1.20082525.1402.78.4.1.9

Abstract

BACKGROUND: Recently, a subpopulation of monocytes expressing Tie2 receptors has been identified, playing an important role in tumor angiogenesis. Selective depletion of Tie2-expressing monocytes in tumor-bearing mice can inhibit tumor angiogenesis. Some of these macrophages have been shown to be located near the tumor blood vessels, forming vessels in these areas paracrinely during the angiogenesis process.

OBJECTIVES: This study aims to investigate the role of putative phosphorylation sites on Tie2 receptor in tumor-associated macrophages connected to human endothelial cells.

METHODS: In this study, we used a series of Tie2 mutants. After transfection of tumor-associated macrophages with these mutants, they were evaluated for physical connection using the surface plasmon resonance technique and by non-contact co-culture of these macrophages with endothelial cells.

RESULTS: Mutation in the tyrosine residues 1106 and 1111 had an inhibitory effect on macrophage binding to endothelial cells, resulting in deterioration of the angiogenic activity of these cells.

CONCLUSIONS: Tie2 receptor and its downstream molecular pathways such as AKT/PI3 have a role in the interaction of tumor-associated macrophages with human endothelial cells, directly (via physical binding) and indirectly (through secretion of factors affecting angiogenesis). This emphasize the importance of the molecular mechanisms of Tie2 receptor activation in the interactions of endothelial cells with tumor-associated macrophages and as an anti-angiogenic therapy for cancer.

Keywords: Angiogenesis, Endothelial cells, Phosphorylation sites, Tie 2, Tumor associated macrophages

Publisher: University of Tehran Conflict of interest: The authors declared no conflict of interest.

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How to cite this article:

Mohseni Z, Nasiri SM, Hoseini Pajooh K, Habibi-Kelishomi Z, Goliaei B. Role of Putative Phosphorylation Sites on Tie2 Receptor in the Interaction between Tumor-Associated Macrophages and Human Endothelial Cells. J Vet Res, 2023; 78(4): 235-246. doi: 10.22059/jvr.2023.354283.3323

Figure Legends and Table Captions

Figure 1. Quantitative analysis of angiogenesis by examining 25 colonies per well.

Figure 2. The average length of each tube (in µm) in five microscopic fields using an image analyzer (Sight DS-L2, Nikon)

Figure 3. Tube formation on matrigel after Tie2 mutantion in (A) all residues, (B) residue 1100, (C) residue 1106, and (D) residue 1111.

Figure 4. (A) Physical interaction of human umbilical vein endothelial cells (HUVECs) with macrophages using surface plasmon resonance (SPR) method; (B) HUVEC culture on SPR sensing gold chips: SPR curve of gold chips before and after cell culture; (C) Sensogram of macrophages with different Tie2 mutations on an HUVEC monolayer.