EBioMedicine 35 (2018) 22–23

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Osteoglycin – A switch from angiogenesis to T-cell recruitment?

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Osteoglycin (OGN)/mimecan is a member of the small leucine rich proteoglycan (SLRP) family. It has been shown to play a role in bone formation and collagen fibrillogenesis and has been implicated in pathological conditions including cardiovascular disease, connective disease and cancer [1]. The structure and function of OGN is variable in normal physiology and pathological conditions and the molecular mechanisms through which it exerts its function are still not clear. In most types of cancer, expression of OGN is markedly down-regulated as compared to the corresponding normal tissues [1]. Available expression data collectively suggest that OGN acts as a tumor suppressor, but functional analysis demonstrating the specific mechanisms through which OGN affects tumor progression is essentially lacking. In this issue of EBiomedicine, Hu and co-authors demonstrate a novel mechanism through which OGN limits tumor growth in colorectal cancer, namely through enhancing T-lymphocyte recruitment [2].

High intratumoral expression of OGN is associated with prolonged patient survival in colorectal cancer, originally attributed to an inhibition of epithelial-mesenchymal transition (EMT) and reduced tumor invasiveness [2]. In the present study, Hu et al. demonstrate a correlation between OGN expression and T-cell infiltration in human tumors by combining expression data from publicly available databases and in-house patient cohorts. A causative relationship was established through over-expression of OGN in a murine MC38 colorectal cancer model, leading to enhanced T-cell infiltration. In parallel, it was found that expression of vascular endothelial growth factor (VEGF) was reduced in subcutaneous MC38 tumors overexpressing OGN as compared to control. The clinical relevance of this observation was confirmed by analysis of TCGA data, showing a negative correlation between OGN and VEGF mRNA expression in colorectal cancer tissue. When incorporated into Matrigel plugs, OGN-expressing MC38 cells induced fewer blood vessels than control MC38 cells, indicating that OGN negatively regulates angiogenesis. Consistent with this, OGN overexpression in MC38 cells inhibited HIF-1α-induced transcriptional activation of VEGF.

OGN is a component of the vascular matrix produced by vascular smooth muscle cells and downregulated by pro-angiogenic factors [3]. Data from a limb ischaemia mouse model show that OGN can indeed act as a negative regulator of angiogenesis under hypoxic conditions [4]. However, the observation that OGN represses tumor angiogenesis in colorectal cancer provided by the study by Hu et al. is novel and provides new understanding regarding its role in repressing tumor growth. Although the relationship between OGN-induced effects on T-cell infiltration and angiogenesis were not experimentally assessed in this study, it is possible that they are functionally connected. High expression of pro-angiogenic factors such as VEGF in tumors represses pro-inflammatory up-regulation of adhesion molecules and chemokines that are necessary for T-cell recruitment [5]. This is at least partially due to a direct interference with NF-κB signaling, markedly attenuating the response to inflammatory stimuli and leading to endothelial anergy [6]. Decreased VEGF expression may therefore boost endothelial activation and enhance recruitment of T-lymphocytes in OGN-expressing tumors.

More than a decade ago, the subtype, prevalence and localization of T-lymphocytes within the tumor was shown to be superior to the classical TNM histopathological staging in predicting clinical outcome in colorectal cancer [7]. The importance of the immunological context of the tumor indicated by this early study has since been confirmed in multiple solid cancer types. Recent successes in boosting the immune response to treat cancer through checkpoint-blockade therapy further underscores that tumor-infiltrating T-lymphocytes have the potential to target malignant cells and limit tumor growth and has sparked immense research efforts in the field of tumor immunology [8]. However, checkpoint-blockade is only efficient in treating a minority of cancer patients. Since the therapy is designed to boost the activity of pre-existing tumor-targeted T-lymphocytes, treatment success strictly depends on efficient recruitment of T-lymphocytes into the tumor. Molecules that alter recruitment of immune effector cells have therefore received considerable interest from the cancer research field both as potential prognostic or predictive factors and as putative targets for pharmaceutical intervention.

The ability of OGN to repress epithelial-mesenchymal transition of malignant cells, block angiogenesis and promote immune targeting of the tumor through enhanced recruitment of T-lymphocyte suggests that it is a potent onco-suppressive molecule in colorectal cancer worth exploring for therapeutic purposes. However, given the general promiscuity of SLRPs in binding to and modulating several signaling receptors, OGNs interaction with cell surface receptors, the affected signaling pathways and the impact on different cell types in the tumor microenvironment requires additional investigation. Therapeutic delivery of OGN into tumor tissue is a challenging obstacle to overcome which has yet to be explored. This may improve immune-targeting of malignant cells and could potentially be used to boost other types of cancer immunotherapy. Further research is required to determine if OGN plays a similar role in regulating angiogenesis and immune

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.07.021.
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https://doi.org/10.1016/j.ebiom.2018.08.020

contexture in other types of cancer, and if its expression can be predictive of an efficient response to cancer immunotherapy.

Conflict of interest

The author declares no conflict of interest.

Acknowledgements

AD is supported by a Senior Investigator Award from the Swedish Cancer Society (CAN 2015/1216).

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