Myeloid cell nuclear differentiation antigen (MNDA) and Human disease

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1. What is MNDA

MNDA, short for Myeloid Cell Nuclear Differentiation Antigen. The protein is mainly found in myeloid cells inside the nucleus and some B-cell lymphomas (Manohar et al., 2020). It is a key regulator of the immune response that operates within the nucleus of a cell and is an important part of your body's defense. It is primarily found in myeloid cells like monocytes and neutrophils. MNDA is essentially a switch for genes that manage apoptosis, which is programmed cell death. MNDA has two big domains: the Pyrin (PYD) domain and the HIN-200 domain(Meng et al., 2024). These 2 domains allow the MNDA protein to connect with DNA and other proteins (Barber, 2011). This is what allows MNDA to control how a gene works. Transportation of the MNDA protein is important because when the body is dealing with something that can cause inflammation or cell death, the MNDA protein is necessary to deal with it properly.

2. MNDA and immune response

MNDA plays key roles for maintaining and inducing the production of type I interferons (IFN-alpha and IFN-beta) in monocytes and plasmacytoid dendritic cells, which are vital for fighting viral infections , such as COVID-19. It does this by regulating the expression of the transcription factor IRF7(Gu et al., 2022).

3. MNDA and Cancer

In cancer, though, especially in tumor-associated macrophages, MNDA can do the opposite and promote cancer growth. This dual aspect shows that MNDA's role is context-dependent.

(1) Diagnostic Tool:

MNDA is highly the expression in marginal zone lymphoma (MZL), can be helpful for differential diagnosis (Manohar et al., 2020). As about 78% MZL is MNDA positive and only about 2.6% positive in Follicular lymphoma (FL).

(2) Prognostic Indicator:

Studies indicate that high levels of MNDA are associated with poor prognosis, serve as a biomarker for aggressive cancers metastasis, and inflammation in patients with hepatocellular carcinoma (HCC)(Meng et al., 2024). MNDA is mainly expressed in M2 macrophages and enhances M2 macrophage polarization (Meng et al., 2024). MNDA had the potential to enhance HCC cell metastasis both in vivo and in vitro via regulating the expression of secretory proteins from M2 macrophages. MNDA promote cancer spread via exosomes. In conclusion, MNDA could play a role in the tumor microenvironment (TME) by M2 macrophages. Targeting MNDA might be exploited as a new strategy to reprogram M2 macrophages with the aim of reducing progression of HCC (Meng et al., 2024). However, MNDA also have anti-tumour role in other cases like lung adenocarcinoma (LA), high MNDA expression activation of various immune cells and is associated with a good prognosis, suggesting MNDA plays a complex, context-dependent role in the immune response to cancer(Bottardi et al., 2024).

(3) MNDA and Apoptosis:

MNDA can also control gene transcription and apoptosis. In neutrophils, MNDA is cleaved by caspase enzymes upon undergoing apoptosis. It then relocates from the nucleus and into the cytoplasm, where it breaks down anti-apoptosis protein Mcl-1, its breakdown induces the neutrophil to die, which helps end inflammation. Abnormalities in this system, as in severe sepsis, are able to

induce neutrophil delays in death and increase disease. In the case of lymphomas like B-cell, MNDA is mainly used to control the anti-apoptosis protein including MCL-1 and BCL-2 proteins by impacting the stability of the two anti-apoptosis proteins(Bottardi et al., 2020).

Research has proven that chemotherapeutic agents influence genotoxic stress. MDNA pivots from its usual place in the nucleolus into the nucleoplasm in CLL and other lymphoid cells. Once it reaches the nucleoplasm, MNDA attaches to chromatin at the Mcl1 and Bcl2 gene regions, influencing the function of RNA polymerase II. This discloses that MNDA directly connects with Mcl1 and Bcl2 precursor mRNAs, helping trigger their quick breakdown when the cell experiences genotoxic stress. The rapid decrease in Mcl1 and Bcl2 RNA levels acts as a post-transcriptional method of promoting apoptosis in CLL cells. In conclusion, these findings clarify previous clinical observations showing that patients with higher MNDA levels usually have a more favorable disease course(Bottardi et al., 2020).

(4) MNDA and Multiple Myeloma

Multiple myeloma (MM) is a plasma cell cancer in the blood. It usually develops from previous stages, starting with Monoclonal Gammopathy of Undetermined Significance(MGUS), with a low level of M-protein and no organ damage, in some cases, development to Smoldering Multiple Myeloma (SMM) with a higher M-protein level and myeloma cell in the bone marrow, without symptoms. The symptomatic MM stages occur as new diagnosis MM (NDMM) including myeloma cells accumulate with end-organ damage. They carry different risks of progressing to active myeloma(van de Donk et al., 2021). MNDA is a protein that plays significant roles in immune regulation, gene regulation, and apoptosis. Xu et al reported MNDA is present in a certain subclass of multiple myeloma cells, and the expression levels have potentially been linked to cell cycle and migration, which advocates involvement in disease progression(Xu et al., 2021).

3. Summary of MNDA's Significant Functions:

Immune response: Induced by interferon alpha, causes cytokine production and immune activation(Gu et al., 2022) .**Transcriptional regulation**: Regulates which genes to activate, including those involved in cell death (Bottardi et al., 2024). **Apoptosis**: Facilitates the degradation of Mcl-1 to allow cell death and resolution of inflammation (Bottardi et al., 2020). **DNA sensing**: Through the HIN-200 domain, it detects DNA inside cells and activates immune signaling (Barber, 2011). **MNDA and Cancer**: It plays an immune evasion roles by enhanceing M2 polarization to facilitate the metastasis of hepatocellular carcinoma (Meng et al., 2024) and also plays anti-tumours role in lung adenocarcinoma (LA) by activation of anti-tumor immune response (Bottardi et al., 2024).

Reference:

Barber, G. N. (2011). Innate immune DNA sensing pathways: STING, AIMII and the regulation of interferon production and inflammatory responses. *Curr Opin Immunol*, *23*(1), 10-20. https://doi.org/10.1016/j.coi.2010.12.015

Bottardi, S., Guieze, R., Bourgoin, V., Fotouhi-Ardakani, N., Douge, A., Darracq, A., Lakehal, Y. A., Berger, M. G., Mollica, L., Bay, J. O., Omichinski, J. G., & Milot, E. (2020). MNDA controls the expression of MCL-1 and BCL-2 in chronic lymphocytic leukemia cells. *Exp Hematol*, *88*, 68-82 e65. https://doi.org/10.1016/j.exphem.2020.07.004

Bottardi, S., Layne, T., Ramon, A. C., Quansah, N., Wurtele, H., Affar, E. B., & Milot, E. (2024). MNDA, a PYHIN factor involved in transcriptional regulation and apoptosis control in leukocytes. *Front Immunol*, *15*, 1395035. https://doi.org/10.3389/fimmu.2024.1395035

Gu, L., Casserly, D., Brady, G., Carpenter, S., Bracken, A. P., Fitzgerald, K. A., Unterholzner, L., & Bowie, A. G. (2022). Myeloid cell nuclear differentiation antigen controls the pathogen-stimulated type I interferon cascade in human monocytes by transcriptional regulation of IRF7. *Nat Commun*, *13*(1), 14. https://doi.org/10.1038/s41467-021-27701-x

Manohar, V., Peerani, R., Tan, B., Gratzinger, D., & Natkunam, Y. (2020). Myeloid Cell Nuclear Differentiation Antigen (MNDA) Positivity in Primary Follicles: Potential Pitfall in the Differential Diagnosis With Marginal Zone Lymphoma. *Appl Immunohistochem Mol Morphol*, *28*(5), 384-388. https://doi.org/10.1097/PAI.0000000000000738

Meng, Y., Zhang, M., Li, X., Wang, X., Dong, Q., Zhang, H., Zhai, Y., Song, Q., He, F., Tian, C., & Sun, A. (2024). Myeloid cell-expressed MNDA enhances M2 polarization to facilitate the metastasis of hepatocellular carcinoma. *Int J Biol Sci*, *20*(8), 2814-2832. https://doi.org/10.7150/ijbs.91877

van de Donk, N., Pawlyn, C., & Yong, K. L. (2021). Multiple myeloma. *Lancet*, *397*(10272), 410-427. https://doi.org/10.1016/S0140-6736(21)00135-5

Xu, J., Wang, Y., Wei, Z., Zhuang, J., Li, J., Sun, Y., Ren, L., Wang, Y., Li, P., Gu, S., Zhang, Y., Jiang, J., Chen, C., Zhang, Y., & Liu, P. (2021). Single-Cell Transcriptomes Combining with Consecutive Genomics Reveal Clonal Evolution and Gene Regulatory Networks in Relapsed and Refractory Multiple Myeloma. *Front Cell Dev Biol*, *9*, 794144. https://doi.org/10.3389/fcell.2021.794144