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The menin conundrum: scaffold proteins, the new frontier.

Adan Rios,[1], Sara Taveras[1], David Marin[2], Anneliese Gonzalez[1].

1. Division of Hematology/Oncology, Department of Internal Medicine.
2. McGovern Medical School, The University of Texas Health Science Center at Houston
3. Division of Cancer Medicine, Department of Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston, Texas.

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

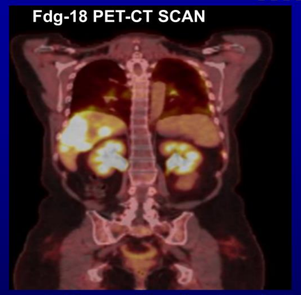
INTRODUCTION

The MEN1 gene encodes menin protein. Menin interaction with MLL1 fusion proteins (MLL1/KMT2Ar) drives mixed lineage leukemias. On the other hand, MEN1 gene mutations cause Multiple Endocrine Neoplasia type I (MEN 1). Menin inhibitors interactions with wild-type or MLL1 fusion proteins have renewed interest in the duality of menin's function and the biology of scaffold proteins in cancer.

SCAFFOLD PROTEINS.

Scaffold proteins tether signaling pathways into complexes localizing the signaling reaction to specific areas in the cell. Mutations of *MEN1* eliminate menin's tumor suppressor activity over endocrine organs resulting in MEN 1 syndrome, a rare heritable disorder with a predisposition to tumors of the parathyroid glands, anterior pituitary, gastrinomas in the duodenum, neuroendocrine tumors, and other tumors. Alternatively, menin can act as a scaffold for pathogenic signal complexes such as KMT2Ar driving Mixed Lineage leukemias.

MEN I AND MGUS





TEST	
SPEP	0.41 g/dl
IFE	Monoclonal gammopathy of IgG-lambda isotype.

- A 43-year-old patient invasive left breast cancer, Her-2-neu negative, strongly ER positive,
- parathyroid tumor, pancreas with NET and liver.

Her father has MEN I which she also had (*MEN1* R465*).

She also had a monoclonal gammopathy of unknown significance (MGUS).

To our knowledge, this is the second case of MGUS associated with MEN I in the medical literature.

AML NET and KMT2Ar

A 41-year-old male with acute myeloid leukemia with monocytic differentiation (MLL) (11q23) MLL gene rearrangement (KMT2A) in 83.5% of myeloblasts.

At bone marrow transplant consultation, noted to have multiple liver lesions. Biopsy revealed a neuroendocrine tumor (NET). Dotatate scan confirmed a somatostatin avid distal ileal NET with nodal metastases.
Underwent a successful allogeneic BMT and is on NET treatment.

Gene sequencing of his NET is in progress.



CONCLUSIONS

Menin is just one of many scaffold proteins.

Most scaffold proteins have not been identified.

Scaffold proteins with menin as its prototype constitutes a new area of research in oncology.

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CONTACT INFORMATION

Adan Rios MD
Division of Hematology /Oncology .
McGovern Medical School.
The University of Texas Health Science Center at Houston.
E-mail: adan.rios@uth.tmc.edu
Cell:713-829-81534