

QUICK FACTS - Menin

What is menin?

Menin is a scaffold protein found in the cell nucleus and plays a direct and important role in transcriptional regulation, cell cycle control and proliferation, apoptosis, and gene expression¹. Additionally, it plays an essential role in oncogenic signaling in multiple cancer types by interacting with transcriptional partners to drive the expression of cell cycle protein regulators, as well as in preventing the replication and expansion of insulin-producing beta cells in the pancreas.

Definitions:

Scaffold protein – a descriptive term (and not necessarily a defined biological class) for proteins that interact with multiple members of a signaling pathway to bring them together and facilitate their function by creating multi-protein complexes.

Transcriptional regulation – transcription is the process of reading genetic material (DNA) and converting it to a message (RNA) that tells the growth/production machinery of the cell what to make. This is a highly regulated process that is affected by many factors.

Cell cycle (or cell division cycle) – the series of events that take place in a cell that cause it to divide into two daughter cells. These events include the duplication of its DNA into the two daughter cells in a process called cell division.

Apoptosis (also called programmed cell death) – a mechanism that allows cells to self-destruct when stimulated by the appropriate trigger.

What does menin do?

Menin is not known to have an active, *individual* function (for example, menin is not an enzyme that has intrinsic catalytic functions), but rather is thought to provide a structure or a scaffold to attach other proteins and organize them in a complex that is necessary to read and transcribe DNA. There are many proteins that bind to menin, and the formation of multi-protein menin-based complexes ultimately enables the DNA reading and transcription process. This reading and transcribing of DNA is a critical step in forming the machinery and duplicating the genetic material necessary for cell replication.

Why is menin important?

Cell replication is critical for an organism to grow, but in some diseases, like in cancer, uncontrolled replication leads to an overabundance of cells that can crowd out necessary, normal tissues and organs, ultimately killing the organism. As such, menin is a key component of such uncontrolled growth pathways in certain solid and liquid tumor types. Inhibition of menin is a potential novel approach not only to new cancer therapies, but also to restoring the ability for the pancreas to resume its insulin production in people with diabetes.

¹ Agarwal SK, et al. *Horm Metab Res* 2005. DOI: 10.1055/s-2005-870139

What proteins does menin interact with in cancer?

Menin binds directly to the mixed lineage leukemia (MLL) proteins. MLL1 gene translocation abnormalities affect approximately 10% of acute leukemias in adults and 70% of acute leukemias in infants. Menin has also been shown to play an essential role in the MYC transcriptional complex, which leads to menin-mediated regulation of MYC target gene expression in cancer cells. MYC is a protein that is thought to regulate cell growth, differentiation, metabolism and death and is often over-expressed in many cancers. MYC is aberrantly expressed or translocated in relapsed / refractory DLBCL and MM. In addition, MYC cooperates with KRAS to cause various types of tumors and to maintain the viability of those KRAS-mutant tumors².

We believe menin provides a scaffold function for several proteins that can trigger abnormal uncontrolled growth, making it a very attractive protein to target for new cancer therapies.

What is menin's role in the pancreas?

In the pancreas, menin interacts with transcriptional partners that drive the expression of cell cycle protein regulators, including those that prevent the replication and expansion of insulin producing beta-cells. Insulin is a hormone that helps the body use glucose for energy and control blood glucose levels. In patients with diabetes, the beta cell mass and function are diminished, leading to insufficient insulin secretion and high blood sugar. Menin is thought to act as a brake on beta cell turnover and growth, supporting the notion that inhibition of menin could lead to the regeneration of normal healthy beta cells. As such, if realized in the clinic, menin inhibition could potentially be a disease-modifying approach for long-term glucose control and amelioration of the comorbidities associated with diabetes.

The normal function of menin is thought to negatively regulate beta cell replication in the pancreas; in this context, inhibition of menin may result in increased beta cell numbers and long-term, disease-modifying control of diabetes.

² Chester E. Chamberlain, et al. Menin Determines K-RAS Proliferative Outputs in Endocrine Cells. J Clin Invest. 2014;124(9):4093-4101. <https://doi.org/10.1172/JCI69004>