Caspase-activated DNase (CAD) as Target to Fight Metastasis

Compounds with CAD inhibitory activity

Technology

Metastasis is often the major cause of death after tumor formation. One of the causes for metastasis is genomic/chromosomal instability which shows as the appearance of so-called micronuclei. Micronuclei have recently been shown to be recognized by the cytosolic DNA-recognition and-signalling pathway orchestrated by the recognition enzyme cGAS and the signal transducer STING. Very recently, it was found that the continuous, spontaneous generation of micronuclei, upon recognition by cGAS/STING, leads to epithelial-mesenchymal transition (EMT), to cytokine secretion, invasion and metastasis.

Experimentally the inventors have shown that sub-lethal activity of mitochondrial apoptosis drives micronuclei formation. Inhibition of mitochondrial apoptosis or of Caspase-activated DNAse (CAD) reduced the number of micronuclei in tumor cell lines as well as the number of chromosomal misalignments in tumor cells and intestinal organoids. CAD can therefore be regarded as a new point of interference to prevent or treat metastasis.

In a screen for compounds with CAD-inhibitory activity, 13 verified hits were identified. All of these compounds showed the expected activity in confirmatory assays. These compounds can be starting points for drug development programs for new treatments aiming at reducing metastasis of tumor cells, preventing or reducing senescence, and reducing inflammation.

Innovation

- A new paradigm to fight metastasis.
- CAD as target to prevent or treat metastasis
- Compounds with inhibitory activity towards CAD

Application

- Treatment or prevention of metastasis
- Preventing or reducing senescence
- Reducing inflammation

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