CMIP in Autoimmunity and Cancers: Friend or Foe

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Editorial

Malignant tumors result from a succession of alterations in genomic and epigenomic patterns, including gene mutations, changes in DNA methylation, post-translational histone modifications, or chromatin structure. Malignancies share several pathogenic features with autoimmune diseases, such as immune dysregulation, genetic and environmental factors. Thus, patients with Sjogren syndrome are more susceptible to develop non-Hodgkin lymphoma, reflecting a disorder of B-cell regulation [1,2]. The risk of cancer development is increased in patients with inflammatory bowel disease [3-5]. However, the mechanisms linking autoimmunity and malignancy leading to paraneoplastic syndromes remain unclear. It is well known that glomerular diseases such as minimal change nephrotic syndrome (MCNS), focal and segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN) are the most frequent renal diseases occurring concomitantly or in close temporal relationship with cancer disease. They are termed paraneoplastic glomerulopathies because the renal disease is not directly linked to tumor burden, progression or metastasis.

Recent observations showing that CMIP (C-maf inducing protein) is overproduced in malignant cells, as well as in podocytes, of patients in whom malignant tumors occurred concomitantly or in close proximity with nephrotic glomerulopathies, such as MCNS and FSGS, has shed new light on the pathogenic connection between cancer and immune diseases. For instance, CMIP has been found overproduced in malignant hematological diseases, such as Hodgkin diseases [6], in lung adenocarcinoma [7] and in some solid tumors (unpublished data). In all these cases, CMIP was highly induced both in malignant cells and in podocytes. However, it is not currently clear whether the expression of CMIP is associated with a good or bad prognosis regarding the malignant disease course.

CMIP is an 86-kDa adapter protein that does not belong to any known family. Its predicted structure includes an N-terminal region containing a pleckstrin homology domain (PH), a middle region characterized by the presence of several interacting docking sites, including a 14-3-3 module, a protein kinase C (PKC) domain, an Erk domain, an SH3 domain similar to the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K), and a C-terminal region containing a leucine-rich repeat (LRR) domain. CMIP contains a nuclear localization site (NLS) near the C-terminus of the PH domain. Thus, CMIP can move to the nucleus but its localization is not clearly restricted to a particular subcompartment. In basal conditions, CMIP abundance is very low in most tissues examined [8,9]. Interestingly, nephrotic syndrome occurs in near 10% of patients with malignant tumors under targeted therapies, mainly those based on receptor tyrosine kinase inhibitors (RTKI). We have shown that RTKI induces in vivo and in vitro high CMIP expression in both lymphocytes and podocytes [10], compromising notably the NF-kB signaling pathway. Because of the limited follow-up, it is also unclear whether increased CMIP abundance in lymphocytes confers a higher sensitivity of tumor cells to RTKI.

There is growing evidence that increased CMIP abundance could affect the function and survival of podocytes [11]. Transgenic mice expressing selectively CMIP in podocytes develop heavy proteinuria without any inflammatory lesions or immune complex deposits [8]. Biochemical studies have shown that CMIP binds the Src kinase Fyn in vitro and in vivo and prevents the phosphorylation of nephrin and the recruitment of N-WASP and Nck, resulting in cytoskeleton disorganization and protein leakage. These findings are supported by in vivo studies showing that silencing endogenous CMIP with RNAi prevents the induction of proteinuria in LPS-treated mice. Podocyte disorders associated with increased CMIP abundance have also been observed in another experimental model of immune-mediated podocyte disease [12].

The implication of CMIP in multiple signaling pathways is likely linked to its particular structure. Thus, overexpression of CMIP induces inactivation of RhoA, downregulation of synaptopodin and loss of stress fibers, while the expression of both integrin-linked kinase (ILK) and Death-associated protein kinase (DAPK) is increased. These perturbations are reversed by cyclosporine, alongside with downregulation of CMIP abundance in podocytes [12]. Remarkably, we have provided evidence of a functional antagonism between CMIP and NF-kB. Using different approaches including chromatin immunoprecipitation, mobility shift and luciferase activity assays, we demonstrated that RelA, a major NF-kB transcription factor, binds to CMIP promoter and inhibits its
activation, while RelA-deficient cells display increase CMIP abundance [10]. Conversely, overexpression of CMIP in differentiated podocytes promotes apoptosis by inducing caspase-3 activation, and upregulation of the pro-apoptotic protein Bax, while decreasing abundance of the anti-apoptotic protein Bcl-2. [11] The inhibitory effect of CMIP overexpression on NF-kB activity is independent of cell type since it has also been reported in several cell lines (Jurkat cells, podocytes, Hela cells), as well as in human peripheral T lymphocytes [8,11,13]. These studies have accumulated evidence to suggest that upregulation of CMIP is harmful to podocytes and support the assumption that CMIP transcription is actively repressed in physiological conditions [14]. However, the signification of CMIP overproduction in tumor cells remains unclear. Because CMIP is an adapter protein displaying multiple effects on signaling pathways governing cell survival and death, it is postulated that CMIP induction in malignant cells could slow down the progression of the disease. However, this hypothesis does not explain why CMIP is concomitantly over induced in podocytes. Much remains to be understood about the pathophysiology of paraneoplastic glomerulopathies. As CMIP induction seems to be at the crossroads of these pathologies, further research addressing this setting will constitute an invaluable tool.

References


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