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Commentary

Mesothelin-Specific Immune Responses and Targeted Immunotherapy for Mesothelin-Expressing Tumors

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Mesothelin is a 40-kDa cell-surface glycoprotein that is normally present on normal mesothelial cells lining the pleura, peritoneum, and pericardium. Moreover, mesothelin has been shown to be overexpressed in several human cancers and correlated with the patient's survival (Einama et al., 2016). The full-length human mesothelin gene (Full-ERC/mesothelin) encodes a 71-kDa precursor protein. The 71-kDa mesothelin precursor is cleaved into two products, a 40-kDa C-terminal fragment (C-ERC/mesothelin) that remains membrane-bound via a glycosylphosphatidylinositol anchor, and a 31-kDa N-terminal fragment (N-ERC/mesothelin, megakaryocyte potentiating factor, MPF), which is secreted into the blood (Einama et al., 2016).

In EBioMedicine, Zhenjiang et al. examined whether there was qualitative tailoring of mesothelin-specific cellular immune responses (Zhenjiang et al., 2017). The authors found that IFN-γ responses to 'mature mesothelin', which means 40 kDa, C-ERC/mesothelin, conditioned by IL-2 and IL-7, were correlated with the survival of patients with brain metastases. Moreover, Zhenjiang et al. showed that increased survival was only observed in association with immune reactivity to the 'mature' (40 kDa, C-ERC/mesothelin) cell-associated part of the mesothelin protein and not with MPF, the N-ERC/mesothelin, part. This suggests that only 'mature' mesothelin expression has a significant role in tumor biology. We showed similar data to demonstrate the biological role of Full-, C-, and N-ERC/mesothelin in the lymphatic invasion of colorectal cancer, using an in vitro lymphatic invasion assay. C-ERC/mesothelin, the 40-kDa membrane-localized fragment, promoted lymphatic invasion by increasing cell adhesion to lymphatic endothelial cells (Kawamata et al., 2014).

Our group investigated mesothelin expression in gastrointestinal cancers using immunohistochemistry (IHC), especially focusing on the localization of mesothelin, i.e., "luminal membrane-positive" and/or "cytoplasm-positive". Luminal membrane positive mesothelin represents 'mature mesothelin', C-ERC/mesothelin, the 40-kDa membrane-localized fragment, and it has a significant function in the aggressive behavior of cancer cells(Einama et al., 2011, 2012; Kawamata et al., 2012, 2014). Based on the findings of this study, mesothelin-specific T-cell responses might occur in patients with brain metastasis to some extent and improve survival better. Further studies are required to characterize the mechanism underlying interactions between brain metastasis and the mesothelin-specific response.

We have many options to detect mesothelin expression, IHC and ELISAs. In IHC, luminal membrane expression of mesothelin represents 'mature' mesothelin (40 kDa, C-ERC/mesothelin) (Einama et al., 2012; Kawamata et al., 2014). Two established ELISAs have been developed to measure the levels of soluble mesothelin-related peptide (SMRP) (Scholler et al., 1999) and megakaryocyte potentiating factor (MPF, N-ERC/mesothelin) (Ito et al., 2014). In this article, the authors performed flow cytometric analysis to evaluate 'mature' mesothelin expression, and showed INF-γ production. Based on these results, I would be interested in the correlation between mesothelin-specific cellular immune responses and established detection tools for mesothelin expression, IHC and ELISA.

Mesothelin is an attractive target for cancer immunotherapy because its normal expression is limited to mesothelial cells, which are dispensable. Several antibody-based therapeutic agents as well as vaccine and T-cell therapies directed at mesothelin are undergoing clinical evaluation (Hassan et al., 2016). Based on this study, in patients who undergo mesothelin-targeted immunotherapies might need to examine the expression status of mature mesothelin (40 kDa, C-ERC/mesothelin). Most patients who express C-ERC/mesothelin in gastrointestinal cancers and ovarian cancer and malignant mesothelioma have a poor prognosis compared with patients

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who do not express C-ERC/mesothelin. In breast cancer, the survival of Her2-positive patients was poor, but now, we have many options for anti-Her2 therapy, and the survival of Her2-positive breast cancer patients is now satisfactory. We need to create 1) established methods to enhance anti-mesothelin specific T-cell responses in vivo, and 2) C-ERC/mesothelin specific immunotherapy, and 3) an optimal treatment regime and schedule for mesothelin targeted immunotherapy.

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Disclosure

The authors have no conflicts of interest to declare.

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