mycophenolate mofetil, etanercept, extracorporeal photopheresis, anti-thymocyte globulin, alpha-1 antitrypsin, mesenchymal stromal cells, everolimus, or sirolimus can be used.

Clinical manifestations of cGVHD may be restricted to a single organ or widespread. The primary manifestations are skin involvement resembling lichen planus or cutaneous scleroderma, dry oral mucosa, ulcerations and sclerosis of the gastrointestinal tract, elevated serum bilirubin, and bronchiolitis obliterans. First-line treatment of cGVHD consists of steroids. For patients with mild cGVHD, localized/topical treatment can be preferred rather than systemic therapy. For initial treatment of moderate or severe cGVHD, systemic treatment with prednisone or methylprednisone at an initial dose of 1 mg/kg body weight/day should be used. The addition of azathioprine, mycophenolate mofetil, cyclosporine, thalidomide, or hydroxychloroquine to prednisone did not improve the response rate or other end-points in randomized trials. If symptoms progress during the first 4 weeks of first-line therapy or there is no improvement in symptoms within 8—12 weeks, second-line therapy should be initiated. For steroid refractory cGVHD patients ruxolitinib can be added to prednisone. Non-pharmacologic therapies such as extracorporeal phopheresis (ECP) has the advantage of being non-immunesuppressive. An immunosuppressive drug can be added to prednisone such as a calcineurin inhibitor or mycophenolate mofetil, but none shown to be effective. İbrutinib which is an inhibitor of Bruton's tyrosine kinase (BTK) has activity against cGVHD.

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Sp08

EVOLUTION OF THE PLEURAL SECRETOME ASSOCIATED WITH PLEURAL METASTASIS

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Malignant pleural effusions (MPE) are characterized by a distinct and complex secretome that varies little between malignancies. To understand the origin and functional significance, we measured 40 cytokines and chemokines in 356 MPE (mainly breast cancer, lung cancer and esophageal cancer), and compared them to benign effusions (n=18) and normal, non-effusate pleural fluid (n=27).

Pleural effusions were collected during therapeutic drainage. Normal (non-effusate) pleural fluid was aspirated during minimally invasive cardiac surgery. Samples were clarified by centrifugation and stored at -80°C until assay. Samples were analyzed with the Luminex platform, using the MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel - Premixed 38 Plex (Cat. No. HCYTMAG-60K-PX38), plus IL-6Rα (Cat. No. HANG2MAG-12K-01), and TGFβ (Cat. No. TGFBMAG-64K-01).

The baseline secretome in normal pleural fluid is dominated by IL-6Rα, CCL2, CXCL10, FGF2, TGFβ1 and CCL22.

Effector cytokines (IFNα, IFNγ, CCL3, TNFα and TNFβ) and most stimulatory cytokines (GM-CSF, TGFα, G-CSF, IL-2, IL-5, IL-7, IL-9, IL-12p40, IL-12p70, IL-3) were absent in NPF.

Benign effusions, whether due to cardiac insufficiency or chronic inflammation (asbestosis without malignancy) resulted in a profound secretomic change, with statistically significant increases in IL-6, TGFβ1, GRO, IL-10 and IL-8, and decreases in FGF2 and IL-15.

All cytokines and chemokines present at elevated levels in benign effusions were also elevated in malignant effusions, with statistically significant increases in G-CSF, CX3CL1, GM-CSF, IFNγ, IL-1TNFα, IL1Rα, CCL4, VEGF, TNFβ, EGF, IFNα, IL-4 and IL-12p40, compared to benign pleural effusions.

Benign effusions can result from an imbalance between hydrostatic and oncotic forces or from inflammation. In both conditions our data indicate a dramatic and consistent change in the pleural environment dominated by IL-6, a highly pleotropic cytokine. When bound to sIL6-Rα, IL-6 induces pro-inflammatory trans-signaling that is markedly stronger than classic signaling and a potent driver of the epithelial to mesenchymal transition (EMT). Additionally, CXCL10, IL-8 and TGFβ1 are known to promote EMT, critical for the maintenance of the normal mesothelium, but dangerous when cancer cells reach the pleural environment, because EMT is associated with cell motility, invasion and therapy resistance.

It is unknown whether prior perturbation of the pleural environment is prerequisite to pleural metastasis, or alternatively, whether chance seeding of the pleura with metastatic tumor leads to secretomic changes similar to those seen benign effusions. In either case, the pleural environment is conditioned to promote tumor growth and inhibit anti-tumor immunity. The presence of cytokines such as VEGF and FGF2 in MPE further condition the pleural environment for tumor growth. The contained nature of the pleural space suggests that local interventions with protein therapeutics to block or augment key cytokines may alter this environment and render pleural metastases susceptible to chemo- or immunotherapy.

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Sp09

INTRAPLEURAL THERAPY TO DRIVE SYSTEMIC ANTI-TUMOR IMMUNITY

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Cancer metastatic to the pleura is uniformly fatal with a median survival of six months and quality of life that is diminished by dyspnea and discomfort. There is currently no curative treatment once metastatic disease has occurred. Current standard of care treatment for malignant pleural effusions (MPE) is exclusively palliative, consisting of drainage, followed by systemic therapy (chemotherapy, endocrine, or immunotherapy). Our institutional experience with systemic immune checkpoint blockers indicates a marginal