Inflammation as a potential therapeutic target in multiple myeloma

Background

Multiple myeloma (MM) is a plasma cell neoplasm in the bone marrow (BM), characterized by paraproteinaemia and clinical symptoms including anaemia, bone destruction, and kidney injury. Despite recent advances in anti-myeloma drugs, MM remains an incurable cancer. There will be a 1.6-fold increase in the number of MM patients from 2010 to 2030 due to population aging, highlighting the pressing need for effective therapy. Recent clinical trial results suggest that immunotherapy will play a key role in disease control of MM. In particular, several immunotherapies have shown remarkable clinical responses that cannot be achieved by conventional chemotherapy. Now that MM immunotherapy has become a very active research area, global multiple myeloma therapeutics will reach a value of USD 37.5 billion by 2024. However, myeloma immunotherapy is still in an exploratory phase in this disease, and further efforts are warranted to achieve durable clinical responses. In-depth understanding the immune microenvironment of MM will provide a clue to identify a new therapeutic target for immunotherapy.

We have made significant contributions to understand the MM immune microenvironment. We firstly revealed the immune microenvironment transcriptome from newly diagnosed 73 myeloma patients, and showed that BM immunosuppressive myeloid cells critically regulate infiltration of effector lymphocytes. Moreover, we demonstrated that the pro-inflammatory microenvironment driven by IL-18 plays critical role for immunosuppression in MM (Cancer Cell 2018). The vicious cycle of inflammation and immunosuppression will be an important therapeutic target in the era of myeloma immunotherapy.

Technology brief

We have established the preclinical platform to assess efficacies of immunotherapy and anti-myeloma drugs, using syngeneic transplantable MM models (e.g., Vk*MYC MM models and a 5TGM1 MM model) and various gene-targeted mice.

In collaboration with French group and local hospitals in Brisbane, we characterized the cytokine profile of bone marrow fluid from 152 newly diagnosed MM patients, and showed that high levels of IL-18 predict poor prognosis independently of known clinical risk factors (Cancer Cell 2018). Our comprehensive profiling of the pro-inflammatory molecules in the MM BM will be an important platform to design a new therapeutic approach.
Summary

- MM-associated inflammation pathway is a potential druggable target to harness anti-tumor immunity.
- Assessing the BM pro-inflammatory mediators (including IL-18) might be helpful to predict immunosuppressive status and/or therapeutic responsiveness to immunotherapy.

Intellectual property

PCT/AU2018/050437 therapeutic compositions and uses therefor

Lead Researcher

Dr Kyohei Nakamura was trained in Department of Hematology and Rheumatology, Tohoku University (Sendai, Japan), followed by postdoctoral training under supervision of Professor Mark Smyth (a world-leading cancer immunologists, QIMR Berghofer).

In collaboration with Dr Ludovic Martinet and Dr Hervé Avet-Loiseau (Cancer Research Centre of Toulouse, France), our blood cancer research team has published impactful works including the immune landscape and the role of IL-18-driven inflammation in MM (Cancer Cell 2018), TIGIT as a key immune checkpoint (Blood 2018), and CD137-based immunotherapy (JCI Insights 2019).

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