Jun regulates monocyte-derived macrophage accumulation and tumour progression.

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Introduction: Macrophages are innate immune cells of haematopoietic origin present in every organ. Given their variety of functions, macrophages are therapeutic targets in many diseases including cancer. Despite the extensive recent research efforts to characterise macrophage origins, the molecular mechanisms regulating the differentiation of tissue macrophages is still poorly defined. Expression of the AP-1 factor, Jun, increases during macrophage differentiation, but its role in macrophage development is still not known.

Materials and methods: To characterise how Jun affects macrophage development and homeostasis, we developed a conditional gene-targeted mouse model with Jun deficiency in the myeloid lineage (JunΔCsf1r).
The roles for Jun during macrophage differentiation was assessed in various tissues at steady-state and during inflammation or tumour development.

Results: in vitro experiments showed that Jun controls CSF1-mediated monocyte to macrophage differentiation, proliferation and survival, from bone-marrow progenitors. Furthermore, in vivo, Jun deficiency limits monocyte-derived CSF1-dependent macrophage accumulation at steady-state in lungs and intestine lamina propria.
Tumour-associated macrophages (TAMs) are thought to play a critical role in cancer progression. We observed that Jun deficiency prevents the differentiation of CSF1-dependent monocyte-derived TAMs and reduces melanoma growth. We further showed that Jun-dependent TAMs play specific trophic functions regulating VEGF availability and inducing blood vessel normalization in melanomas. In contrast, during acute inflammation, Jun was dispensable for the recruitment and maturation of monocyte-derived inflammatory macrophages.

Conclusion: Our results identify Jun as an important regulator of monocyte-derived CSF1-dependent macrophage differentiation, without altering monocyte effector functions. In a melanoma model, we showed that Jun-dependent macrophages have important tumour-promoting functions. Therefore, Jun is a selective regulator of CSF1-dependent macrophage development, which is redundant during inflammation. These observations could help to define novel approaches to selectively target macrophage differentiation, without altering monocyte-dependent immune responses.

Keywords : Jun, macrophage maturation, tumour-associated macrophages, Csf1,
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