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POINT OF VIEW

Macrophages and c-Myc cross paths

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ABSTRACT
The c-Myc transcription factor has recently been proposed as a bona fide M2 macrophage marker. Although this finding represents a major step forward in the identification of different macrophage subsets, it also opens up the potential for speculation concerning the possible functions of c-Myc in macrophages and the implications for health and disease.

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Macrophages are immune cells that mediate the killing of pathogens, tissue remodeling, angiogenesis, inflammation, resolution of inflammation and when their activity is deregulated, inflammatory disease processes. They are also involved in tumor growth.[1] The c-Myc transcription factor (c-MYC in humans), either directly or by regulating the expression of other proteins, controls cell proliferation, apoptosis and cell survival, tissue remodeling, angiogenesis, cell metabolism, and production of inflammatory and anti-inflammatory cytokines, and it also participates in cell transformation.[2,3] The wide range of processes involving both macrophages and c-Myc made it inevitable that at some point the paths of these two heavyweights of biology would cross. Indeed, c-MYC has been shown to be expressed *in vitro* by human macrophages classed as M2,[4,5] a macrophage activation status associated with anti-inflammation, angiogenesis and tissue remodeling. In addition, c-MYC expression has been detected *in vivo* in certain types of human tumor-associated macrophages (TAMs), which have an M2-like macrophage activation status.[4] In the murine context, c-Myc expression in M2 macrophages was initially suggested by its role in regulating murine TAM development and activity *in vitro* and *in vivo* as well as by the reduced inflammation-resolving activity *in vivo* of macrophages lacking c-Myc.[6,7] A recent study by Jablonski et al.[8] using RNA microarrays has definitively identified c-Myc as a marker of murine M2 macrophages *in vitro*

It is important to note that, in human macrophages studied *in vitro*, c-MYC expression is restricted to the M2 phenotype and is almost undetectable in M0 (resting) and M1 (inflammatory) macrophages.[4] However, murine M0 macrophages express small but detectable levels of c-Myc.[8] This could be because human M0 macrophages do not proliferate *in vitro*, whereas murine M0 macrophages retain their ability to proliferate in culture, perhaps because of the presence of c-Myc. Indeed, both wild-type murine M0 macrophages in the presence of a c-Myc inhibitor and murine M0 macrophages lacking c-Myc show reduced proliferative activity (unpublished data). This observation may shed light on one of the hottest topics of recent years: are all macrophages derived from circulating monocytes or are their numbers dependent on proliferation within tissues?

Another issue that has generated controversy in recent years is the fact that murine macrophages and their markers do not always resemble what is seen in humans. For example, one of the most important murine M2 markers, arginase I, has been shown to be a less reliable marker for human M2 macrophages. In this regard, a similar observation made by Jablonski et al.[8] stands out, regarding the expression of SLC40A1, the iron exporter ferroportin. Although in humans its expression correlates with c-MYC expression in M2 macrophages,[9,10] in murine studies its expression appeared to be downregulated in M2 compared with M0 macrophages.[8] However, it is important to remember that murine M0 macrophages express a low level of c-Myc, which could be mediating the expression of SLC40a1 in these cells. What seems clear is that c-Myc does not support the expression of SLC40a1 in murine M2 macrophages, suggesting that c-Myc has different functions (not limited to proliferation) in murine M0 and M2 macrophages.

The characterization of c-Myc as a murine M2 marker represents a great improvement in the identification of different macrophage populations *in vivo* in health and disease. However, further investigations are needed to understand when and why c-Myc is expressed and what its functions are in macrophages. Several interesting questions arise from these studies: for example, does c-Myc also promote the acquisition of the M2 phenotype by inhibiting M1 markers; does c-Myc play different roles depending on the macrophage maturation status; what is the role of c-Myc in macrophage metabolism; and is c-Myc detectable in macrophages expressing c-Myc dependent proteins?

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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