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Roberta Piva

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Roberta Piva; Department of Biomedical and Specialty Surgical Sciences; University of Ferrara; Ferrara, Italy; Email: piv@unife.it;
http://dx.doi.org/10.4161/cc.27865

The role of Retinoblastoma (RB) family members (RB1, RB2/P130, and P107) as cell cycle progression inhibitors is well established in many areas of biology, including cancer biology and developmental biology.[1,2] Beyond its role in early cell cycle decisions, RB proteins regulate chromatin structure, metabolism, cellular differentiation, and senescence/apoptosis phenomena.[3,4] Only recent studies revealed a crucial role for RB-mediated signaling on fate determination of stem cells and progenitor cells.[5] The novel functions assigned to RB family members in controlling several aspects of stem cell biology open an important scenario not only in terms of basic research, but also for regenerative medicine applications and therapeutics interventions. It is, in fact, very important to attribute new roles to known proteins, to identify new molecular targets to facilitate the development of cellular therapeutics to replace damaged, diseased, or aged tissues.

Stefania Capasso and colleagues have now elucidated the role of RB family members in the commitment of mesenchymal stem cells (MSCs) toward adipogenic differentiation.[6] Interestingly, in a previous paper, these investigators showed that the silencing of RB1, but not of RB2/P130, is deleterious to MSCs. It, in fact, decreased proliferation, promoted the accumulation of DNA damage, and impaired stem cell properties with an increase in senescence and loss of self-renewal properties.[7]

In this new work, a number of issues are of particular interest. First, the authors use human multipotent precursors such as MSCs from bone marrow (hBMSCs) to study the entire adipocyte differentiation process and not cell lines or committed adipose tissue progenitors, such as pre-adipocytes. This, in part, may attempt to explain controversial data regarding RB and different stages of adipogenesis. The distinction between progenitor cells and stem cells might sometimes seem vague; however, long-term ability to self-renew, which is a stem cell's typical characteristic, allows us to study, in its entirety, the balance between proliferative potential and appropriate differentiation. This aspect is mostly critical when cell cycle control proteins are under investigation. In addition, it is particularly relevant to demonstrate the adipogenic potential of MSCs derived from bone marrow, improving the concept that bone marrow adipose tissue (BMAT) is a metabolically active tissue under a strict control.[8]

The use of MSCs from a human source is preferable, as it allows to better mimic the physiological microenvironment, helps to elucidate the molecular mechanisms that occur in vivo, and, finally, provides useful information for clinical application. Therefore, such a kind of investigation has an added value compared with those performed on murine experimental models that would be less convincing in interpreting the onset of human diseases. It is important to underline that disorders caused by alteration of adipose tissue metabolism, including diabetes, obesity, and osteoporosis, may benefit from appropriate therapeutics developed in in vitro adipogenesis studies.

Second, the authors used gene-silencing approach for assessing and characterizing the function of the 3 members of the retinoblastoma family. This technology, which turns off a specific gene by transient (siRNA) or stable (shRNA) transfection, can lead to improvements in understanding the role of specific genes during a cell differentiation program. In addition, it is emerging as a powerful tool to promote tissue regeneration through the possibility to control the expression of activators or inhibitors of a lineage-specific signaling pathway. The authors assessed and optimized lentivirus vector-mediated genetic modification of hBMSCs to demonstrate a functional effect mediated by RB1, RB2/P130, and P107 silencing. By using this challenging approach, the authors provide evidence that RB2/P130, and not only RB1, play a critical role in adipogenesis, demonstrating that commitment of hBMSCs to adypocyte lineage is facilitated by RB1 and RB2 knockdown. However, RB-silenced cells feel that a gene that also plays an important role in the cell cycle is missing: consequently, they do not come out definitively from cell cycle and do not reach the terminal differentiation. It is possible that retinoblastoma proteins play a complex role in adipogenesis as well as in other differentiation processes supported by microenvironmental niche of the adult stem cells. Only further in vivo studies will reveal their specific contribution in the intricate balance between self-renewal, proliferation, differentiation, and exhaustion signals, which, as a whole, are crucial for cell fate decision.

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