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Editorial

On the Origin of Cells

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Abstract: While non-blood cell lineage has been studied for decades by developmental biologists, only recently has it been considered in disease. This is partly due to a lack of suitable reagents in experimental models, but it is also the result of a failure to understand the ability of cells to move or differentiate in pathological environments. This Editorial gives a quick overview of the Special Issue "Cell Fate Decisions in Development and Disease" and underscores the importance of understanding the mechanisms of cell fate determination and lineage.

Keywords: cell fate; cell lineage; stem cells; fibrosis

What are the origins of each cell in the body? This is a question that developmental biologists have been studying for decades using various experimental organisms including fruit flies, zebrafish, leeches, sea urchins, chick embryos and mice. With certainty, we know that all cells are derived from the fertilized oocyte, but after that, things get complicated. What is a newer consideration is the role of cell lineages in human disease. Physicians have understood for many years that tissues and organs change in many ways after injury or illness. Definitions have been coined in the attempt to describe how these tissues change. Terms such as "remodeled", "hypertrophic", "hyperplastic", "thickened" *etc.* are standard definitions in pathology, but what do these words really mean? Many assumptions are built into these pathologic concepts, without evidence. For example, a tissue is considered hyperplastic if cell size is normal and the overall tissue increases in size. However, can we tell the difference

between hyperplasia due to local cell proliferation or hyperplasia due to cell invasion and subsequent proliferation of invasive cells?

How do we define cells in pathologic human tissues? Mostly this has depended on investigation of biopsies or post-mortem tissue analysis using standard histological approaches. In some cases, antibodies can be used and cell identity can be inferred from the expression of particular markers. This is a powerful tool, but it is a flawed approach because while antibodies can identify the differentiated form of cells they do not tell us about their origin. For example, in pulmonary arterial hypertension (PAH) the vessel wall becomes hypertrophic, with thickening of the vascular endothelium and adventitial layer. This is accompanied by the formation of plexiform lesions that contain cells that co-express markers of endothelial and smooth muscle cells. The assumption was made for many years that these cells were derived locally from other endothelial and smooth muscle sources. Recent lineage tracing studies in mice demonstrated that both cell types were derived from endothelial precursors [1]. Others more recently have wondered if blood derived cells also contribute to the vascular wall in PAH. Lineage tracing experiments in rats using transplantation of dye labeled cells [2] showed that remodeled arteries in PAH contain cells from both blood and endothelium. This was also observed in the heart when the origin of fibrotic cells was investigated in scar formation after myocardial infarction. Here fibrotic cells were derived both from pre-existing cardiac fibroblasts and from bone marrow derived cells [3]. These studies show that when a tissue is diseased, cell lineages from near and far contribute to the pathology of the organ.

Why is this important? First, as our understanding of how organs and tissues remodel in various pathologies has increased, our therapies to treat these conditions have not improved. For example, the ability of inhaled nitric oxide (NO) to act as a vasodilator was discovered in the early nineties and its use to treat PAH became the standard of care. However, once pulmonary arteries are remodeled, NO does not have the ability to stall or reverse the fibrotic changes to the vessel wall. Thus it is clear that to make new breakthroughs in PAH, and other fibrotic diseases, we will need to better understand how tissues are altered and what molecular pathways play a role in the cellular changes that occur.

In the case of PAH or myocardial scar formation, we are likely interested in approaches that prevent cells from differentiating or reversing a differentiated state. Another issue to consider is that of pathologies caused by the inability of progenitors to contribute to a tissue after injury. An example of this is in the brain where oligodendroglial progenitors (OLPs) are lost or "stalled" in their ability to contribute to remyelination in periventricular leukomalacia or multiple sclerosis [4,5]. In this case resident OLPs are prevented by the injury to differentiate into mature oligodendrocytes. The hallmark of this is the accumulation of OLPs and loss of mature oligodendrocytes along white matter tracts. It is known that activated Wnt signaling can disrupt OLP maturation and that at least in one case, administration of a Wnt antagonist, XAV939, to mice promoted OLP differentiation after a demyelinating injury [6]. Thus, with an understanding of the lineage and the signaling pathways that regulate it, we can begin to appreciate how to manipulate the lineage in our favor and treat the previously untreatable condition.

It is now generally accepted that many tissues and organs contain some kind of undifferentiated progenitor cell, or at the very least some type of cell that has stem cell-like properties when grown in tissue culture. However, the normal function of these cells is poorly understood. Are these cells important for maintenance of an organ over a lifetime? Or do they lie dormant only to be activated

after some kind of injury? Could these cells become maladaptive in disease and contribute to the complexity of the diseased tissue? As our understanding of these issues increases it will be critical to understand how resident stem cells contribute to disease. Then, we can develop strategies to either block the contribution of cells (e.g., in fibrosis) or to promote the contribution of cells (e.g., in demyelination).

This issue will cover a wide range of topics under the umbrella of cell lineage, both in normal development and in disease. The underlying theme is that these contributions are submitted by some of the leading research groups in the field of cell lineage. While the issue cannot cover the entire range of subjects, I hope that it can inspire the readers to consider the ideas presented by the authors, and hopefully to carry out new work that will break down barriers that lead to medical breakthroughs.

Conflicts of Interest

The author declares no conflict of interest.

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