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Review article

Genetic tools for identifying and manipulating fibroblasts in the mouse

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ABSTRACT

The use of mouse genetic tools to track and manipulate fibroblasts has provided invaluable in vivo information regarding the activities of these cells. Recently, many new mouse strains have been described for the specific purpose of studying fibroblast behavior. Colorimetric reporter mice and lines expressing Cre are available for the study of fibroblasts in the organs prone to fibrosis, including heart, kidney, liver, lung, and skeletal muscle. In this review we summarize the current state of the models that have been used to define tissue resident fibroblast populations. While these complex genetic reagents provide unique insights into the process of fibrosis, they also require a thorough understanding of the caveats and limitations. Here, we discuss the specificity and efficiency of the available genetic models and briefly describe how they have been used to document the mechanisms of fibrosis.

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Contents

1. Fibrosis . . . 67
2. Fibroblast definition . . . 67
   2.1. Fibroblast reporter mouse lines . . . 67
   2.2. Cre indicator/reporter systems . . . 68
   2.3. Additional considerations when using reporters and *Cre* technology . . . 68
3. Tissue resident fibroblasts . . . 73
   3.1. Cardiac fibroblasts . . . 73
      3.1.1. Cardiac fibroblast reporter mouse lines . . . 73
      3.1.2. Cardiac fibroblast Cre mouse lines . . . 73
   3.2. Kidney fibroblasts . . . 74
      3.2.1. Kidney fibroblast reporter mouse lines . . . 75
      3.2.2. Kidney fibroblast/pericyte Cre mouse lines . . . 75
   3.3. Liver fibroblasts . . . 76
      3.3.1. Liver fibroblast reporter mouse lines . . . 76
      3.3.2. Liver fibroblast/pericyte/HSC Cre mouse lines . . . 76
   3.4. Lung fibroblasts . . . 76
      3.4.1. Lung fibroblast reporter mouse lines . . . 77

Abbreviations: αSMA, α smooth muscle actin, ACTA2; αV integrin, alpha V integrin; ADAM12, A Disintegrin And Metalloproteinase 12; ADRP, adipocyte differentiation-related protein; AV, atrioventricular; BAC, bacterial artificial chromosome; CCl4, carbon tetrachloride; CD90, cluster of differentiation 90; Cre, bacteriophage P1 recombinase; DDR2, discoidin domain receptor tyrosine kinase 2; Dtr, diptheria toxin receptor; ER, estrogen receptor; FGF10, fibroblast growth factor 10; FoxD, forkhead box D1; FoxJ, forkhead box J1; FSP1, fibroblast specific protein 1, S4100A; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GI, gastrointestinal; Gli1, Gli family zinc finger 1; GSK3β, glycogen synthase kinase 3 beta; HDAC3, histone deacetylase 3; hGFAP, human glial fibrillary acidic protein; HSC, hepatic stellate cells; IHC, immunohistochemistry; kb, kilobase; Klf5, kruppel-like factor 5; lacZ, β-galactosidase gene; LAD, left anterior descending; loxP, locus of cross-over in P1; Lrat, lecithin-retinol acyltransferase; mCrem, merCremer; mGFAP, mouse glial fibrillary acidic protein; MSC, mesenchymal stem cell; Neo, neomycin resistance; NG2, neural/glial antigen 2; PAC, P1-derived artificial chromosome; PDGFRα, platelet-derived growth factor receptor, alpha; PDGFRβ, platelet-derived growth factor receptor, beta; PPARγ, peroxisome proliferator-activated receptor gamma; Ptch1, patched1; RFP, red fluorescent protein; RNA, ribonucleic acid; rtTA/tTA, tetracycline-controlled transactivator; Shh, sonic hedgehog; Tbx4, T-box 4; Tbx18, T-box 18; Tbx20, T-box 20; Tcf4, transcription factor 4; Tcf21, transcription factor 21; TGFβ, transforming growth factor beta; tk, thymidine kinase; UUO, unilateral ureteral obstruction; VSMC, vascular smooth muscle cells; Wt1, Wilms tumor 1

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3.4.2. Lung fibroblast/pericyte Cre mouse lines . . . 77
3.5. Skeletal muscle fibroblasts . . . 78
3.5.1. Skeletal muscle fibroblast reporter mouse lines. . . . 78
3.5.2. Skeletal muscle fibroblast/pericyte Cre mouse lines . . . 78
3.6. Signaling dependent fibroblast lines. . . . 78
4. Concluding remarks. . . . 78
Funding sources . . . 79
References . . . 79

1. Fibrosis

Fibrosis, the deposition of extracellular matrix in response to injury, inflammation, and aging, can be either reparative or reactive. The organs that commonly exhibit fibrosis include the heart, kidney, liver, and lung (Zeisberg and Kalluri, 2013; Rockey et al., 2015). Despite the fact that a chronic fibrogenic response ultimately leads to organ dysfunction and failure, accounting for an estimated one third of natural deaths worldwide (Zeisberg and Kalluri, 2013), few therapeutic options have been identified to slow or reverse the detrimental effects of fibrogenesis (Zeisberg and Kalluri, 2013; Rockey et al., 2015). Although many forms of injury have been used to induce and study fibrosis in animal models, currently the reagents to trace and assess the cellular and biochemical pathways eliciting the scarring process are limited and complicated. One of the purposes of this review is to describe the reagents that are currently being used to understand fibrogenesis within the mouse.

2. Fibroblast definition

One of the key issues to understanding fibrosis is delineation of the role of the fibroblast. This endeavor is complicated, as the fibroblast is poorly defined and sometimes considered immature in regards to its differentiation status (Alberts et al., 2002). Anatomically, a fibroblast is described as a connective tissue cell that produces extracellular matrix (Alberts et al., 2002). Within this definition there are two main classifications: the adventitial fibroblast that surrounds blood vessels and the interstitial fibroblast that is not closely associated with any specific structure. The terms mesenchymal and stromal cell are often used interchangeably and indicate a cell present within connective tissue. The production of extracellular matrix is not an apparent requirement for these definitions. Another term requiring definition is pericyte. Originally, a pericyte was described as a cell that shares a basement membrane with an endothelial cell, but this strict, ultra-structural definition has gradually morphed into a more ambiguous definition relying on proximity to a capillary and expression of surface and structural proteins including PDGFRβ, NG2, α smooth muscle actin (αSMA), and desmin (Armulik et al., 2011).

Within the field of organ fibrosis, there is considerable controversy over the origin of the cell responsible for reactive fibrosis. These disagreements partially stem from the fact that identification of these cells relies on expression or up regulation of genes including vimentin, collagen, and αSMA (reviewed in (Xu et al., 2014; Travers et al., 2016; Krenning et al., 2010)). Specifically, the term myofibroblast was coined due to a pronounced increase in expression of αSMA in collagen producing cells within injured tissue (Petrov et al., 2002; Eyden, 2008; Gabbiani et al., 1972). While a definition based on gene expression is convenient, it restricts identification retrospectively and may represent only a subpopulation of cells. This type of distinction would ignore resident populations of fibroblasts that may be quiescent or not expressing high levels of αSMA. Recent studies using methods to developmentally label fibroblasts raise the issue that αSMA staining underestimates the total population of fibroblasts present after injury (Ali et al., 2014). For the purpose of this review, we will routinely use the term “activated fibroblast” to describe the cell populations that respond to injury via proliferation, αSMA expression, and/or collagen production. We will not use the term myofibroblast as it relies heavily on the expression of a single marker.

Adding to the confusion is the fact that many organs have multiple populations of resident mesenchymal cells capable of producing extracellular matrix. These are often identified using different cellular markers, and nomenclature between organ systems is not consistent. Therefore, in this review at the beginning of each organ section, we will outline the cell types considered to have fibroblast-like qualities. Although genetic tools have been used to trace non-resident sources of fibroblasts, especially those arising from bone marrow-derived cells, for the purpose of this review, we will restrict the discussion to tissue resident fibroblast populations within the heart, kidney, liver, lung, and skeletal muscle. For further reading on tools to investigate other sources of fibroblasts the reader is referred to the following studies (Okabe et al., 1997; Ogawa et al., 2006; Visconti et al., 2006; Hashimoto et al., 2004; McDonald et al., 2015; Kisseleva et al., 2006; Higashiyama et al., 2009).

The purpose of this review is to summarize the current tools available to study the dynamic and enigmatic cell population known as the fibroblast with a focus on the use of genetically engineered mice to identify, follow, and manipulate tissue resident fibroblast populations. We hope that by presenting information for multiple organs, the reader will be able to identify the most appropriate reagents for their experimental system. Due to the scope of this review we will focus only on resident fibroblast and pericyte populations. For more details on other cell types, please refer to these organ specific reviews that are available for heart (Moore-Morris et al., 2015), kidney (Romagnani et al., 2015; Kramann et al., 2013a; Duffield and Humphreys, 2011), liver (Xu et al., 2014), and lung (Rawlins and Perl, 2012).

2.1. Fibroblast reporter mouse lines

A key component of tracking a cell population in vivo is having a reliable and reproducible method for identifying the cells of interest. Mouse lines expressing reporter genes under the control of transcriptional response elements specific to fibroblasts are a sensitive and efficient way to track these cells. Such reporter genes generally come in two varieties: enzymes with colorimetric substrates or fluorescent proteins. Typically, these lines are generated either by insertional transgenesis (transgenic), where the transgene is injected into the pronucleus of a fertilized oocyte, or by gene targeting (knock-in), where the reporter is introduced in an endogenous gene locus to take advantage of regulatory elements of the host gene. Tables 1 and 2 outline available mouse lines that have been used to identify and track fibroblasts in various organs.

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