

Review

Metabolic Reprogramming of Fibroblasts as Therapeutic Target in Rheumatoid Arthritis and Cancer: Deciphering Key Mechanisms using Computational Systems Biology Approaches

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Abstract: Fibroblasts, the most abundant cells in the connective tissue, are key modulators of the extracellular matrix (ECM) composition. These spindle-shaped cells are capable of synthesizing various extracellular matrix proteins and collagen. They also provide the structural framework (stroma) for tissues and play a pivotal role in the wound healing process. While they are maintainers of the ECM turnover and regulate several physiological processes, they can also undergo transformations responding to certain stimuli and display aggressive phenotypes that contribute to disease pathophysiology. In this review, we focus on the metabolic pathways of glucose and highlight metabolic reprogramming as a critical event that contributes to the transition of fibroblasts from quiescent to activated and aggressive cells. We also cover the emerging evidence that allows us to draw parallels between fibroblasts in autoimmune disorders and more specifically in rheumatoid arthritis and cancer. We link the metabolic changes of fibroblasts to the toxic environment created by the disease condition and discuss how targeting of metabolic reprogramming could be employed in the treatment of such diseases. Lastly, we discuss Systems Biology approaches, and more specifically, computational modelling, as a means to elucidate pathogenetic mechanisms and accelerate the identification of novel therapeutic targets.

Keywords: Fibroblasts; Rheumatoid Arthritis; Cancer; Metabolic Reprogramming; Glycolytic Switch; Systems Biology; Computational Modelling

1. Introduction

Fibroblasts were initially described during the 19th century by Virchow [1] and Duval [2] as the most common cell type from connective tissue. They also exhibit a round, large pale and flat nucleus with prominent nucleoli, indicating a very active RNA metabolism [3]. Fibroblasts are known to be essential for a significant number of physiological functions. They produce extracellular matrix proteins (collagen, glycosaminoglycans, fibronectin, laminins, and proteoglycans) and produce the structural framework – stroma – for tissues [4]. They induce epithelial differentiation, regulate inflammation [5], and play a critical role in wound healing by migrating to the damaged tissue [6]. Fibroblasts are widely known to display remarkable phenotypic plasticity with the ability to adapt quickly and efficiently to their environment when activated by appropriate stimuli. For instance, it has been acknowledged that fibroblasts can play a significant role in disease pathogenesis by presenting complex phenotypes and functions according to the biological context. Indeed, some fibroblasts (*e.g.* gingival [7], dermal [8], lung [9], cardiac [10] and synovial fibroblasts [11]) can express innate immune receptors to sense pathogens and present antigens, contributing to the immune response [12]. However, relatively few studies have

considered regulating fibroblasts' functions by developing new therapeutic targets. More efforts are needed to understand the critical role of fibroblasts in disease pathogenesis [13].

2. The Role of Fibroblasts in Rheumatoid Arthritis

In the joint synovium, fibroblasts represent the primary stromal cells. They ensure the structural integrity of synovial sublining and lining by forming a layer thick as one or two cells, interspersed with tissue-resident macrophages [14]. Fibroblasts guarantee nutrient supply and secrete hyaluronic acid and lubricin (two essential constituents of synovial fluid) responsible for lubricating the joints [15,16]. They are also responsible for producing the nonrigid extracellular matrix of the synovial fluid, rich in type 1 and type 2 collagen, helping wound healing and damaged tissue reparation [12]. Many studies in Rheumatoid Arthritis (RA) focus on fibroblasts as these cells play a significant role in disease pathogenesis. RA is a chronic autoimmune disease affecting approximately 1% of the population. The pathogenesis of the disease includes synovial hyperplasia or pannus, which consists of the accumulation of macrophages and fibroblast-like synoviocytes (RASFs) [4,17–19], resulting in enhanced invasiveness and destruction of adjacent cartilage and bone [17–19]. RASFs differ from normal, healthy fibroblasts in their organization, morphology and gene expression pattern. Indeed, this stressful microenvironment of inflamed tissues, where concentrations of crucial nutrients such as glucose, glutamine, and oxygen are not always available [20] leads fibroblasts to be "activated" in order to increase their exchange with other synovial cells and acquire an aggressive phenotype which is described in Figure 1.

At this point, RASFs have reduced contact inhibition, express altered levels of adhesion molecules, cytokines, chemokines and matrix-degrading enzymes, causing cartilage damage and mediating the interaction with neighbouring inflammatory and endothelial cells, affecting the bone *via* regulation of monocyte to osteoclast differentiation [21]. RASFs support the development of the hyperplastic RA synovium as tertiary lymphoid organs (TLOs) by interacting with immune cells like T cells and B cells, producing several mediators and organising ectopic (tertiary) lymphoid-like structures (ELs) [22]. They are also resistant to apoptosis and have an increased ability to migrate and invade periarticular tissues, including bone and cartilage, contributing to their destruction [11,19]. RASFs can also be considered as primary drivers of inflammation, angiogenesis and cell growth [19]. They disturb the homeostatic balance between leukocyte recruitment, proliferation, emigration and death, leading to a persistent leukocyte infiltration [21].

In this way, RASFs are no longer considered as passive bystanders, but as active players in RA pathogenesis and sustained chronicity, and RASF-directed therapies could become a complementary approach to currently used immune-focused therapies.

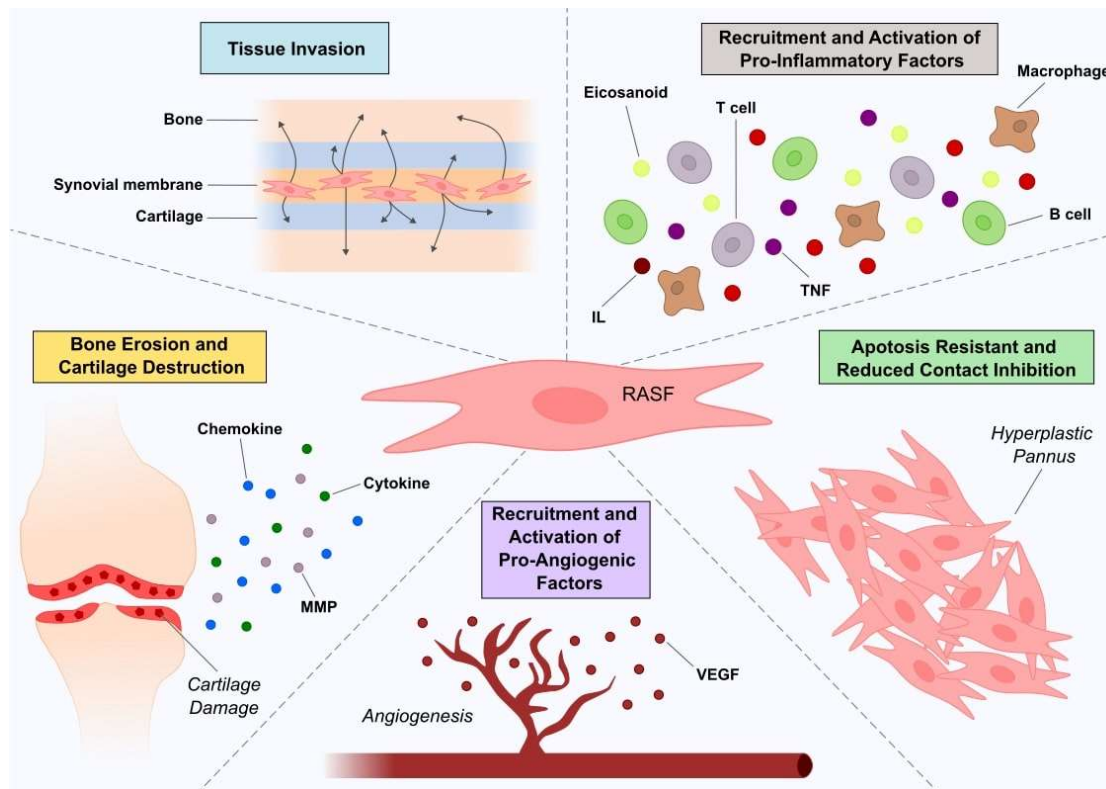


Figure 1. Roles of Rheumatoid Arthritis Synovial Fibroblasts in Rheumatoid Arthritis Pathogenesis. Inspired by “Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors”, Bottini N. & Firestein G.S, 2013, *Nat. Rev. Rheumatol.*, 9, 24-33.

3. The Role of Fibroblasts in Cancer

The cellular environment surrounding cancer cells is mainly composed of the extracellular matrix, immune and endothelial cells, blood vessels and fibroblasts, constituting the structural scaffold to the internal tissues [23]. All together, they form the tumour microenvironment, also known as the tumour stroma [24].

In the cancer field, the importance of the stromal microenvironment in disease has been recognised for years. It is widely accepted that cancer develops as a result of genetic and epigenetic alterations in clonal cells and that these cells' growth, survival and metastasis are regulated by stromal and cancer cell interactions [25]. Also, studies in human lung, breast, colon and prostate cancer have unequivocally demonstrated a key role for stromal cells – so-called Cancer-Associated Fibroblasts (CAFs) – in the disease initiation as well as in the architecture and growth mechanics of the developing tumour [26] as it is summarized in Figure 2.

Several *in-vivo* studies provide evidence of CAFs' significant roles in disease progression. Mice tumour transplantation experiments indicated that CAFs promote cancer cell proliferation, angiogenesis, invasion, and metastasis. In particular, tumours formed after cancer cells transplantation with CAFs are more malignant than tumours developed by transplanting cancer cells alone or with healthy fibroblasts [27,28]. Also, co-implantation of pre-malignant prostate epithelial cells with CAFs prompts epithelial cells malignant transition and proliferation [29]. An apparent interrogation lies in the underlying mechanisms leading to fibroblasts' activation and transformation into CAFs. The main hypotheses are based on autocrine and paracrine mechanisms resulting in secretion of cytokines, chemokines and growth factors by the stromal microenvironment, including the Transforming Growth Factor β (TGF- β), Platelet-Derived Growth Factor (PDGF), Insulin-Like Growth Factor I and II and Granulocyte macrophage-colony Stimulating Factor (GM-CSF) [26,30–32]. They will regulate disease-

relevant gene expression (fibronectin, PAI-1 and cyclin-dependent kinase inhibitors) via specific signalling pathways simulations such as Serine/Threonine Kinase Receptors (RSTK) or the Signal Transduction and Activation of Transcription (STAT) family [33,34] which will ultimately contribute to the expression of a metastatic phenotype by cancer cells, such as increased local growth and invasiveness [35,36].

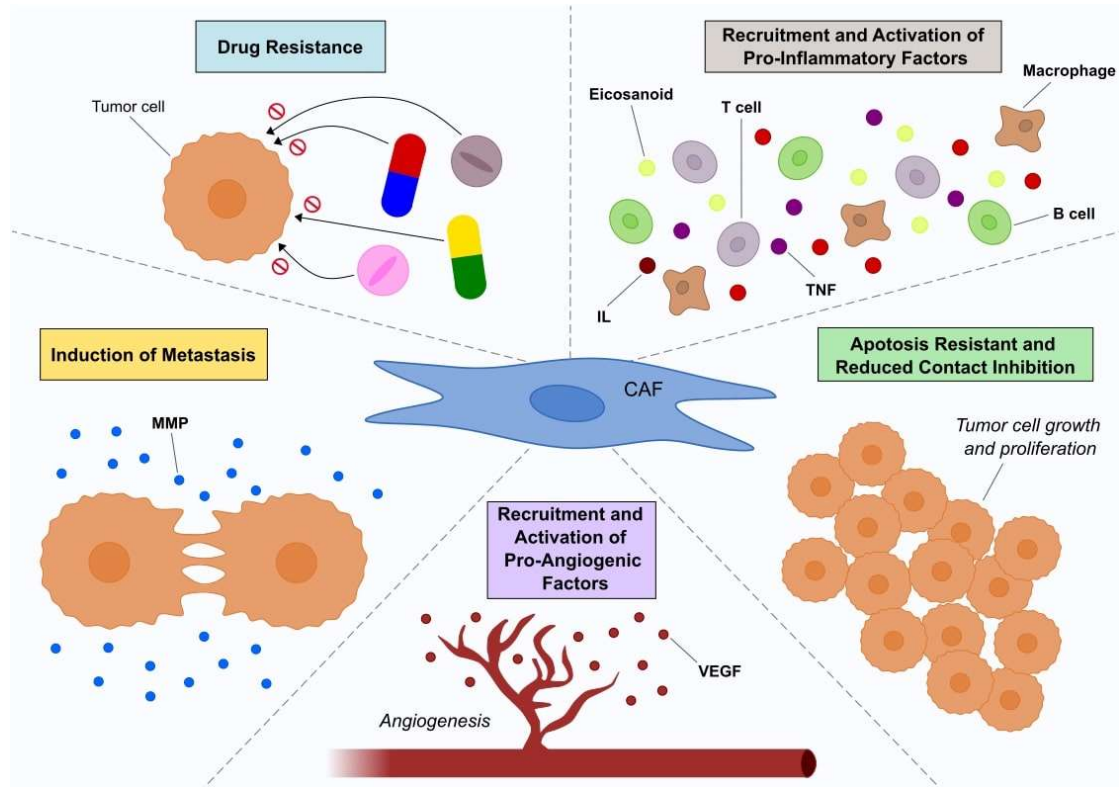


Figure 2. Roles of Cancer-Associated Fibroblasts in Cancer Pathogenesis

4. Shared Features of Rheumatoid Arthritis Synovial Fibroblasts and Cancer-Associated Fibroblasts

Proliferating and aggressive fibroblasts not only seem to be one of the key features in several inflammatory conditions, including RA [3,11,15,16,21,37] but also in cancer [21,25,38–40]. It appears that fibroblasts modify their phenotypic profile not only to adapt to the new environment and survive but also that this adaptation leads to progressive amplification of the disastrous characteristics of the associated diseases as these cells transform from passive responders to key disease effectors.

Obvious parallels can be drawn between RASFs and CAFs [21]: they both are apoptosis-resistant, show a high proliferation rate, secrete matrix metalloproteinases (MMPs), cytokines and chemokines, respond to stimuli like Il6, TNF, TGF- β , are exposed to hypoxia and elevated ROS levels, and – a critical property – express an increased glucose metabolism. Indeed, both RASFs and CAFs are prone to metabolic reprogramming leading to a glycolytic switch. This feature could prove to be critical in identifying the molecular links between metabolic reprogramming and fibroblasts activation, opening new lines of research and the potential development of new treatments [41,42].

5. Metabolic Reprogramming as an Alternative Survival Pathway in Disease

In normal cells, the most common way to generate energy is through oxidative phosphorylation (OXPHOS) in which ATP molecules are produced by the transfer of electrons from NADH or FADH₂ to O₂ by a series of electron carriers [41]. In contrast, in order to keep up with their high proliferation rate, their continuous growth and their high energy request, some cells can switch their metabolism.

The main pathways involved in this adaptation seem to be aerobic glycolysis, glutaminolysis, mitochondrial biogenesis and activities such as the production of reactive oxygen species and Ca²⁺ retention. These pathways provide cells not only with the necessary energy but also with crucial materials to support large-scale biosynthesis, rapid proliferation, survival and invasion [43]. The complex mechanisms behind the metabolism reprogramming observed in highly proliferating cells, and their relevance to disease is the topic of several recent studies [41]. Elucidating why proliferating cells with access to oxygen would deprive themselves of the majority of the ATP that can be produced from glucose metabolism *via* the OXPHOS pathway in the mitochondria by converting pyruvate into lactate rather than acetyl-CoA has been challenging. These studies showed that the use of glycolysis rather than OXPHOS allows faster production of ATP. Besides, this shift also provides several metabolic intermediates to other signalling pathways: ribose-5-phosphate and glycine for nucleotide biosynthesis and citrate for lipid synthesis. In other words, proliferating cells using glycolysis do not convert all the glucose into pyruvate; they use a fraction of it in the tricarboxylic acid (TCA) cycle, thus providing precursors for pathways in need of TCA cycle intermediates to produce fatty acids and amino acids [41,43].

5.1. Metabolic Reprogramming of Fibroblasts in the Rheumatic Joint

Several studies have shown that RASFs activation and the subsequent joint damage are associated with altered metabolism of carbohydrates, proteins, lipids, and nucleic acids [41]. Carbohydrate metabolism is a biochemical process essential for supplying energy to living cells. Glucose, the most important carbohydrate, is first transported into the cell through Glucose Transporter 1 (GLUT1) and then broken down via glycolysis and specific metabolic enzymes to generate pyruvate. Afterwards, it will either enter into the TCA cycle and OXPHOS to generate ATP or it will be converted to lactate by Lactate Dehydrogenase (LDH) [42]. Glucose metabolism seems to be significantly enhanced in joints with arthritis and involved in RA pathology. The local lower glucose levels and a higher ratio of lactate to glucose in the RA synovial tissue, as well as the enhanced level of lactate in RA synovial tissue compared to non-inflamed synovial tissue suggest an increase in anaerobic cellular metabolism in RA patients [44]. Shift from OXPHOS to glycolytic ATP production is a common feature of activated and reactive cells like fibroblasts. Microenvironmental factors in RA joints may contribute to this shift: Hypoxia-Inducible Factor-1 α (HIF1 α), which is a transcription factor induced in hypoxic environments found in RA joints and lead to enhanced glycolytic activity in fibroblasts cells. HIF1 α regulates some genes involved in glucose metabolism, GLUT1 and LDH that are upregulated in RASFs. The activation of glycolysis by HIF1 α contributes to RASFs' survival, myeloid recruitment, angiogenesis, and migration and invasion.

Furthermore, HIF1 α effects on glucose metabolism lead to an increased expression of inflammatory mediators that maintain interactions between RASFs and immune cells [45]. Hypoxia and inflammation also lead to the production of pro-inflammatory cytokines, and MMPs, mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF- κ B), and phosphoinositide-3-kinase (PI3K)/AKT in RASFs. These molecules regulate glucose metabolism through the upregulation of GLUT1, the phosphorylation of rate-limiting glycolytic enzymes, including 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB) and Hexokinase 2 (HK2). JAK/STAT signalling pathway, which is known to activate RASFs, also contributes to glucose uptake and hexokinase2 (HK2) expression [44].

Since many crosstalks are involved, other signalling pathways contributing to glucose metabolism such as pathways related to the glutamine and choline metabolism could also be affected in RASFs [44].

5.2. Metabolic Reprogramming of Fibroblasts in Cancer

Cancer-associated fibroblasts (CAFs) are the primary non-cancerous stromal cell type in the tumour's microenvironment and express an aggressive phenotype. One of the most critical features of solid tumours is the metabolic reprogramming that leads to changes of bioenergetics and biosynthesis

in both tumour cells and CAFs, contributing to the adaptation to hypoxia and hypo-nutrient conditions [46]. As cancer cells and tumour microenvironment form a network in tumour tissues, the crosstalk between cancer cells and CAFs is associated with cell metabolic reprogramming that contributes to CAFs activation, cancer growth, its progression and evasion from cancer therapies [32]. In particular, CAFs undergo a metabolic switch from OXPHOS to glycolysis [47]. By doing so, CAFs allegedly fuel biosynthetic pathways of cancer cells and contribute to tumour development [48]. This dependence on aerobic glycolysis is called the Warburg effect.

According to Yu *et al.* [47], three main hypotheses can account for the preferential use of the glycolysis pathway by CAFs. The first hypothesis is based on the production rate of ATP – essential for cancer cells proliferative growth – which is higher through glycolysis than OXPHOS [49]. The second and third hypotheses are based on the action of glycolytic intermediates, both necessary for the biosynthetic needs of rapidly proliferating cells, but also to maintain adequate levels of reduced forms of glutathione enabling resistance to chemotherapeutic agents [50,51].

This metabolic reprogramming is a complex process: several pathways and mechanisms have been suggested to allow cancer cells and CAFs to sustain the high glycolytic flux, but further studies are needed to shed light on this topic. The first focus is on the Hypoxia-Inducible Factor-1 α (HIF1 α), considered as a master regulator. Indeed, HIF-1 α is associated with the upregulation of several genes directly related to the glycolytic pathway such as glucose transporters (*e.g.* GLUT1, GLUT3) and glycolytic enzymes (*e.g.* HK1, HK2), promoting glycolytic flux and tumour development [52,53]. In cancer cells, HIF-1 α is activated and maintained in many ways. It is widely acknowledged that growth factors are overproduced during tumorigenesis and activate transcription factors, including HIF-1 α . Its regulation is ensured by oncogene (*e.g.* TGF- β) activation and tumour suppressor (*e.g.* p53) inactivation in cancer cells [54]. The rapid tumour growth itself induces hypoxia and ROS accumulation, also maintaining HIF-1 α activity. Finally, the absence of miRNAs keeps promoting aerobic glycolysis by targeting glycolytic enzymes and regulating HIF-1 α [47,55]. Phosphofructokinase-1 (PFK1) and Phosphofructokinase-2 (PFK2) are also recognised as significant players of glycolysis. According to Hamanaka *et al.* [50], the expression of PFK2 is upregulated in cancer cells and promotes fructose-2,6-bisphosphate production, which acts as an allosteric activator of PFK1 to overcome negative allosteric feedback inhibition of PFK1 by high ATP levels and regulate glycolysis. Finally, the end product of glycolysis – pyruvate – is converted by Lactate Dehydrogenase (LDH) in lactate, accompanied by regeneration of NAD⁺, both essential in maintaining glycolysis [56].

6. Metabolic Pathways as Therapeutic Targets in Rheumatoid Arthritis Synovial Fibroblasts and Cancer-Associated Fibroblasts

Metabolic reprogramming and the associated glycolytic switch seem to play central roles in the regulation of RASFs and CAFs phenotypic changes leading them to acquire an aggressive phenotype. RASFs differentiation to cells characterised by enhanced proliferation and resistance to apoptosis contributes to the chronicity of RA and the sustained inflammation in the joints. CAFs differentiation and their crosstalk with cancer cells contribute to tumour growth, progression, invasion to adjacent tissues, and resistance to therapy.

In this context, focusing on the metabolic reprogramming and the glycolytic switch regulating RASFs and CAFs transformation constitutes a promising field for discovering therapeutic targets. Indeed, different approaches have been employed, and a handful of glycolytic enzymes involved in RASFs and CAFs transformation have already been identified and targeted. They were shown to reduce bone and cartilage damage [44], as well as tumour growth [57]. Considering that many parallels have been demonstrated between RASFs and CAFs phenotype and metabolic profiles, it seems plausible that some therapeutic targets may be comparable. Indeed, literature search regarding the targeting of metabolic pathways and more specifically, the glycolytic ones in RA and cancer revealed many similarities in potential therapeutic targets. Several such matching targets are presented below and summarized in Figure 3 and Table 1.

A direct approach would be to disrupt glucose transporters (GLUTs) to prevent glucose entry, which has been shown to work successfully in RASFs [58,59] and CAFs [60–65]. Similarly, disturbance of monocarboxylate transporter (*e.g.* MCT1 and MCT4) was shown to reduce RA severity [59,66–68], as well as inhibition of tumour growth and CAFs recruitment in cancer [38,55,61,69–79]. The use of Hexokinase 2 (HK2) inhibitors such as Lonidamine has also shown clinical success in RA [80], and in the cancer field [61,81]. Moreover, a 3-bromopyruvate treatment allowed a considerable reduction of the severity of RA repercussions in several murine arthritis models [67,80,82–85] and metastatic suppression in cancer [61,86–89].

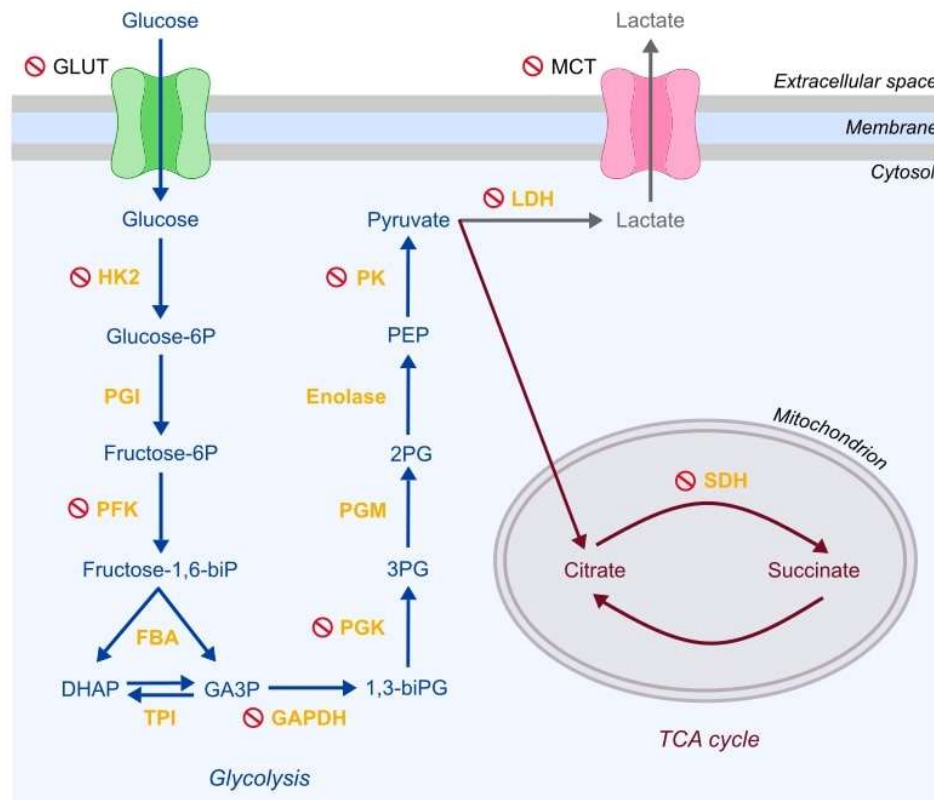


Figure 3. Metabolic Targets in Rheumatoid Arthritis and Cancer Therapeutic Strategies. Transporters are shown in black, glycolytic intermediates in blue, tricarboxylic acid (TCA) cycle intermediates in red and enzymes in yellow. Compounds currently recognized as therapeutic targets are marked with a red stop sign.

Targeting the Phosphofructokinase (PFK) enzyme – responsible for the conversion of fructose-6-phosphate to fructose-2,6-bisphosphate – has also been studied since it reduces glucose uptake, GLUT4 translocation, and glycolytic flux which reduces the production of lactate. PFK's inhibition led to the slowdown of RASFs migration [58,90,91] and showed promising anticancer effects by suppressing glycolytic flux [92]. Studies on Phosphoglycerate Kinase (PGK) – a glucose metabolism enzyme – inhibition showed a decrease in RASFs proliferation, migration and the production of pro-inflammatory mediators [83]. In a different study, PGK inhibition increased tumour cells ability to overcome therapy resistance [93]. The targeting of Glyceraldehyde 3-phosphate Dehydrogenase (GAPDH) enzyme – responsible for catalysing the very first step of glycolysis – is also being studied in RA to evaluate potential beneficial effects [59]. According to Ganapathy-kanniappan *et al.* [89], inhibiting GAPDH affects tumour glycolysis by blocking the most important energy-producing step. The inhibition of Pyruvate Kinase Isozyme M2 (PKM2) has been studied in RA [58,59] for its anti-inflammatory property, as well as in cancer [57,94,95] where it is involved in the bypass of cancer cells

drug resistance. Finally, studies regarding Lactate Dehydrogenase (LDH) inhibition showed promotion of inflammation resolution in RA synovial explants [96] and in cancer [61,69,79,97–108] where it has been shown to reduce tumour progression and is suspected of reversing glycolysis.

Table 1. List of Drugs and Compounds Targeting Rheumatoid Arthritis Synovial Fibroblasts and Cancer-Associated Fibroblasts Metabolism. Common drugs and compounds are marked with an asterisk.

Metabolic Target	Drug or Compound	
	Rheumatoid Arthritis Synovial Fibroblast	Cancer-Associated Fibroblast
<i>HK2</i>	3-Bromopyruvate* [67,80,82–85] 2-deoxyglucose* [67] Lonidamine* [80] Tofacitinib [96]	3-Bromopyruvate* [61,86–89] 2-deoxyglucose* [61,109] Lonidamine* [61,81] T-Lipo-3-BP [87]
<i>GLUT</i>	WZB117* [59] Tumour Necrosis Factor- α inhibitor [58]	WZB117* [64] Fasentin [65] Phloretin [60–63]
<i>MCT</i>	Metformin* [59,66,67] MCT4-siRNA [68]	Metformin* [55,61,72,73] Quercetin [74,75] NAC [69,75–79] α -Cyano-4-hydroxycinnamic [70,71,73] Acetylcysteine combined with Topotecan [38,76]
<i>LDH</i>	Tofacitinib [96]	FX11 [61,69,102] Oxamate [79,103] Quinoline 3-sulfonamides [104] Gossypol [105–108,110] Galloyflavin [98,99] NHI [97,100,101]
<i>PGK</i>	PGK1-SiRNA [83]	adenovirus-shPGK1 [93]
<i>PK</i>	TEPP-46 [59] Tumour Necrosis Factor- α inhibitor [58]	Shikonin and its analogues [94] Alkannin [57] PKM2-siRNA [95]
<i>PFK</i>	3 PO* [58] PFK15 [90,91] PFKFB3-SiRNA [91]	3 PO* [92]
<i>GAPDH</i>	Heptelidic Acid [59] Tumour Necrosis Factor- α inhibitor [58]	3-Bromopyruvate* [88,89]
<i>SDH</i>	Saponin [111] Dimethyl Malonate [112]	3-Bromopyruvate* [88]

7. Computational Systems Biology Approaches

Delineating the complex interplay of the biological processes that underlie diseases, as well as the mechanisms of action of potential drugs, is not a trivial task. [45]. Systems Biology, and more specifically, network biology, has proposed the use of networks to represent cellular processes and interactions between biomolecules, and graphical languages (notation schemes) have been developed to formalise such representations. The Systems Biology Graphical Notation (SBGN) standard includes three languages, namely Activity Flow (AF), Entity-Relationship (ER) and Process Description (PD) [113]. Standardised networks are graphical representations of disease mechanisms that can be constructed either employing top-down approaches, like reverse engineering using machine learning algorithms and omics data or using a bottom-up approach, starting with text mining and literature curation.

Computational Systems Biology combines networks and mathematics to produce dynamical models of the biological systems. With systems modelling, researchers can perform *in-silico* simulations testing various experimental settings, like *knock-out* or *knock-in* experiments in a short amount of time and generate hypotheses that can then be tested *in-vitro*. Various formalisms can be used serving different modelling purposes. Kinetic modelling is usually employed for well-characterized systems for which kinetic data are available for model organisms. Discrete modelling is usually employed for building qualitative predictive models. Either way, dynamic models can give information and insights about the emergent behaviour of the system of interest, help elucidate pathogenetic mechanisms and help design better and more efficient experiments [113].

7.1. Graphical Representations of Molecular Pathways in Rheumatoid Arthritis Synovial Fibroblasts and Cancer-Associated Fibroblasts

In the RA field, a fully annotated, expert validated, state-of-the-art knowledge base in the form of a molecular map has been published recently, illustrating the molecular and signalling pathways involved in disease pathogenesis [114,115]. However, this map is not cell specific as it includes experiments in different cell types such as mononuclear cells, synovial fibroblasts, macrophages and chondrocytes. Due to the extensive annotations, it is possible to opt for fibroblast specific interactions, extract and visualise the corresponding network (synovial fibroblasts are the most frequent cell type in this RA map, covering a total of 45% of the cells).

Regarding cancer-related mechanisms, several attempts to create cancer-specific graphical representations have emerged, such as the Cancer Cell Map Initiative [116] or the Human Tumor Atlas Network [117], regrouping several detailed molecular and cellular maps. Although those maps focus essentially on the tumour microenvironment, fibroblasts are poorly represented. The Atlas of Cancer Signalling Networks (ACSN) [118] is a web-based resource of biological maps depicting molecular processes in cancer cells and the tumour microenvironment. It includes a CAFs dedicated map, representing the molecular interactions involved and the role of such cells. It is separated into different functional modules, including fibroblasts and their activation (e.g. "inflammatory signalling pathways", "interaction with tumour cells", "markers of fibroblast activation").

These molecular maps represent well-curated knowledge with different layers of disease or cell specificity. They can serve as templates for omic data visualisation, and can also be analysed as complex graphs, in terms of topology and structure, revealing interesting properties about the network organization. Moreover, the functional analysis of graph components and modules can offer insights into the pathways affected in different experimental datasets. However, these maps are mainly focused on signalling events and the corresponding metabolic pathways are often absent or underrepresented. To the best of our knowledge, cell-specific metabolic reconstructions are not available yet, but efforts to reconstruct a generic human cell metabolic network have been ongoing with the creation of the ReconMap [119] based on the Human Metabolic Atlas [120]. The Human Metabolic Atlas resource integrates open source genome-scale metabolic models (GEMs) of human and yeast and provides detailed biochemical information for reactions, metabolites, and genes. All model components are also

associated with standard identifiers, for a more straightforward interface with external databases, such as the Human Protein Atlas.

Regarding ReconMap, access through the Virtual Metabolic Human (VMH) database allows easy navigation and search of information on human and gut microbial metabolism along with links to hundreds of diseases and nutritional data. However, these metabolic reconstructions are often too focused on downstream events and completely lack upstream regulators that would link these networks to signalling cascades and gene regulation. Creating integrative networks is still a key challenge in the field [121].

7.2. Computational Models for Rheumatoid Arthritis Synovial Fibroblasts and Cancer-Associated Fibroblasts

All living systems are, by definition dynamic. Thus, graphical representations of molecular and cellular networks can provide useful but limited information on the mechanisms underlying disease pathogenesis, progression, severity or even response to treatment. In this context, dynamical studies and models can reveal critical information about the system's global behaviour under various conditions by performing *in-silico* simulations, perturbation experiments, hypotheses-testing and predictions.

Regarding RA, some mathematical models have been developed lately, but most of them are not cell-specific or do not account for metabolic reprogramming. An Ordinary Differential Equation (ODE) RA-specific model with two variables was proposed to study interactions and dynamics of pro-inflammatory and anti-inflammatory cytokines as these molecules can modulate the severity and duration of the associated inflammation [122]. The Entelos Rheumatoid Arthritis PhysioLab platform [123], a large-scale mathematical model was also developed to explain the inflammatory pathway and bone erosion process in RA joints. This model was used to predict the therapeutic effect of membrane receptors and intracellular targets. It was developed using *in-vivo* and *in-vitro* studies on primary human cells and animal cells which increases uncertainty margins. ODEs models, including time-evolution, were also used at a tissue-level to describe the amount of bone erosion in RA joints [124]. An effort to incorporate spatial and temporal aspects of biological mechanisms behind RA was also made by building a Partial Differential Equations (PDEs) model to explain the roles of different cell types including inflammatory fibroblasts in the degradation of cartilage in RA joint [125]. It was used to evaluate the efficacy of drug combinations, including experimental ones. Synovial membrane and cartilage are represented as two adjacent planar layers, and the state of the disease is qualified by how much the cartilage layer has decreased. It is a simplified geometry compared to how RA is currently evaluated (*e.g.* radiographic images, mathematical scores). More complex models are also available to capture the randomness of biological mechanisms. One of the few models that account for stochastic environmental/genetic effects (exposure to specific infections or toxins, random mutations in somatic genes involved in cellular growth and differentiation, DNA repair, or in immune mechanisms) is a 1-equation mathematical model describing three rheumatic disorders, including RA disease [126]. This model was used to analyse the age-specific incidence of these diseases and showed that only a small number of random events need to occur in a predisposed population to allow the emergence of rheumatic disorder. Although various approaches and models have been developed to understand RA pathogenesis better, most of them lack cells and species specificity. As more evidence is accumulating about the critical role of fibroblasts in disease pathogenesis and sustained inflammation, disease and cell-specific integrative human-data-based models are urgently needed to understand RASFs' role from a systems perspective.

Similarly, viewing cancer as a dynamic system composed of heterogeneous actors interacting at different scales is not a new idea [127,128]. Several mathematical models have been proposed throughout the years to shed light on several physiological features specific to cancer cells. A mechanistic pan-cancer pathway model was developed to study stochastic cell fate responses to several drugs and mitogens [129]. An agent-based model of cancer cells was also proposed [130], proving the effects of seeding rate and location in tumour growth. In the same interest, a partial differential equation

predictive model of metastatic spreading has been presented [131]. Interactions of cancer cells with the tumour microenvironment were also modelled using a four-compartment dynamic model [132] or an agent-based model [133]. However, the main focus of mathematical modelling in the cancer field has revolved around the study of tumour cells' metabolism. Interactions mediating metabolic changes were investigated by a hybrid cellular automaton model, highlighting the need of cancer cells for phenotypic adaptations [134]. Another suggested approach involved the use of an ordinary differential equation-based kinetic model to study the evolution of several metabolites and their inhibition [135]. Special attention was given to explaining the Warburg effect: a genome-scale computational study allowed identification of metabolic targets inhibiting cancer migration [136] while other models tried to elucidate the strategy behind the glycolytic switch [137,138]. Regardless of such developments and even though fibroblasts have demonstrated a critical role in tumorigenesis, they have been overlooked and modelling approaches focusing on CAFs' behaviour and the associated metabolic reprogramming are sorely lacking. A very recent study [139] tries to fill this gap by proposing an agent-based dynamic model to further investigate the role of CAFs. Nevertheless, it focuses almost exclusively on their crosstalk with cancer cells and does not consider metabolic reprogramming.

8. Perspectives

In RA, the recently published RA map [115] can serve as a basis for the building of a regulatory graph and the associated logical model. Initially, researchers were set to build a large-scale Boolean dynamical model for the study of RA fibroblasts' activation based on the RA map and a previously published, more generic model on fibroblasts [140]. However, more recent developments such as the map-to-model framework published by Aghamiri *et al.* [141], using CaSQ, a translation tool from static molecular maps to executable Boolean models, was also tested successfully on the RA map. Nonetheless, as the map is not cell-specific, additional work is needed to ensure the desired cell-specificity of the model. This map-to-model conversion could also be applied to the CAFs map from the Atlas Cancer Signalling Networks [118] to provide a first, coarse-grained, large scale executable model.

As cells are complex systems with a variety of biological processes intertwined, models of CAFs and RASFs should focus on integrating multiple layers of information that would allow the connections between extracellular stimuli, intracellular signalling cascades, transcription factor activity and gene expression regulation and, last but not least, metabolic pathways. Studying complex biological processes requires an integrative approach that spans across several layers of biological information (genomic, epigenomic, metabolomic, proteomic in bulk and single-cell level) taking advantage of the wealth of multi-omics data being available and accessible [142]. This kind of approach would lead to conceptual developments and discoveries and help unravel biological mechanisms that regulate health and disease [143]. The advancements of high-throughput techniques and the wealth and availability of multi-omics data can support multiscale modelling approaches to address complex interactions between different organisation levels in the systems [143,144].

The whole-cell modelling community is making a significant effort towards this direction as whole-cell dynamical models of human cells are a main goal and one of the highest bets in the field of Systems Biology. Whole cell models could provide a significant aid to researchers and clinicians to better understand cell biology, pathophysiology and response to treatment [145]. The first whole cell model was published in 2012 [146] and described the prokaryotic cell of *mycoplasma genitalium*, but despite the important challenges to create a human whole cell model, technological advancements, dedication and building on experience shows that this type of models will soon become feasible. As cells are not isolated in the human body, another important aspect in systems modelling is the necessity to describe the interplay between several cell types in order to gain a better insight on the system of interest (*i.e.* the immune system). Multicellular modelling is essential for capturing interactions between cells of interest and their neighbours, in health and disease states. There are key challenges in the field, not yet fully addressed that need to be tackled in order to obtain robust,

reproducible, standardized and data-driven multicellular models. To overcome these challenges and go beyond the current state-of-the-art, the field of Systems Biology should orient its effort towards a community-driven ecosystem of interoperable data, software, and computational modelling platforms [147].

9. Conclusions

As highlighted previously, building multiscale and multicellular models has proven to be arduous and laborious because of the complexity of biological systems [148] and the computational cost associated with *in-silico* simulations and system perturbations. Nevertheless, technological developments in High-Performance Computing (HPC) [149] and initiatives like the recently launched European HPC/Exascale Centre of Excellence in Personalised Medicine (PerMedCoE) open avenues for cell-level simulations in HPC/Exascale [150].

To bridge the technological and methodological gaps between organ, cell and molecular simulations, collective and interdisciplinary efforts are needed to pave the way for bigger, more complex and closer to reality models of the biological systems. Detailed computational models of fibroblasts that can span across multiple biological layers, including metabolic reprogramming, could become valuable tools in understanding disease pathogenesis in autoimmunity and cancer. Deciphering metabolic reprogramming could help researchers find new ways of actively reversing pathological states to healthy, quiescent states, leading to novel pharmaceutical targets and treatments.

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