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Immunometabolic Landscapes of Chronic Pathology: A Comparative Review of Macrophage Plasticity, Ferroptosis, and Therapeutic Interventions in Triple-Negative Breast Cancer and Osteoarthritis

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Abstract

Background: Triple-Negative Breast Cancer (TNBC) and Osteoarthritis (OA) represent two distinct poles of chronic pathology: one a highly aggressive, metastatic malignancy and the other a chronic, debilitating degenerative condition. Despite their clinical differences, both are driven by profound dysregulation in the local microenvironment, characterized by aberrant macrophage polarization, metabolic stress, and inflammatory signaling.

Methods: This review synthesizes recent literature to map the molecular intersections between TNBC progression and OA pathogenesis. We analyzed mechanisms of chemoresistance in TNBC, specifically focusing on the VCP-TMEM63A-DERL1 axis and ferroptosis, and contrasted these with synovial inflammation and matrix metalloproteinase (MMP) activity in OA. Furthermore, we evaluated the therapeutic efficacy of soybean-derived bioactive peptides and saponins across these conditions.

Results: Analysis reveals that macrophage plasticity is a critical driver in both diseases. In TNBC, HLF-mediated regulation of ferroptosis and tumor-macrophage crosstalk facilitates progression, while in OA, macrophage polarization drives synovial fibrosis and cartilage degradation. Crucially, soybean bioactives, including genistein and Bowman-Birk inhibitors, demonstrate significant potential in modulating these pathways by suppressing pro-inflammatory mediators (IL-6, NF-kappaB) and regulating autophagy.

Conclusion: There is a remarkable convergence in the signaling nodes governing TNBC and OA. Targeting the inflammatory microenvironment through metabolic modulation—specifically via ferroptosis induction in cancer and

inflammatory suppression in arthritis—offers a promising therapeutic avenue. Natural bioactive compounds warrant further investigation as potent, pleiotropic agents capable of addressing these shared molecular targets.

Keywords: Rheumatoid Arthritis (RA), VAS — visual analog scale, disease-modifying antirheumatic drugs (DMARDs), Annexin A1 (ANXA1), interleukin-6 (IL-6), Disease Activity Score in 28 Joints (DAS28)

1. Introduction

The global burden of disease has shifted dramatically in recent decades, characterized by a dual rise in aggressive malignancies and chronic degenerative conditions. According to systematic analyses for the Global Burden of Disease Study, these pathologies account for a significant proportion of disability-adjusted life years worldwide [13]. Among these, Triple-Negative Breast Cancer (TNBC) stands out as a clinical entity defined by its lack of estrogen, progesterone, and HER2 receptors, rendering it unresponsive to conventional hormonal therapies and particularly reliant on cytotoxic chemotherapy and emerging immunotherapies [6]. Concurrently, Osteoarthritis (OA), once viewed merely as "wear and tear" of the cartilage, is now understood as a complex, whole-joint disease driven by low-grade, chronic inflammation, with the synovium playing a pivotal role in pathogenesis [14].

While TNBC and OA appear clinically distinct—one a rapid, lethal neoplasm and the other a slow, progressive degradation of joint integrity—recent molecular insights suggest they share profound commonalities in their underlying immunometabolic landscapes. Both diseases are characterized by a hostile microenvironment where the behavior of resident immune cells, particularly macrophages, dictates disease trajectory. In TNBC, the tumor microenvironment (TME) orchestrates immune evasion and drug resistance through mechanisms such as autophagy and ferroptosis [2, 3]. In OA, the synovial microenvironment perpetuates tissue destruction through the release of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines like IL-6 [17, 22].

A critical area of emerging research lies in the intersection of these pathways and the potential for pleiotropic interventions. Natural bioactive compounds, specifically soybean-derived peptides and saponins, have shown remarkable capacity to modulate these very pathways—suppressing inflammation in arthritis while potentially sensitizing cancer cells to treatment [25, 27]. This article aims to synthesize the latest evidence regarding these shared molecular mechanisms. By juxtaposing the aggressive metabolic rewiring of TNBC with the chronic inflammatory signaling of OA, we explore the hypothesis that targeting macrophage plasticity and metabolic regulators (such as ferroptosis and autophagy) offers a unified strategy for treating diverse chronic pathologies.

2. Methods

This narrative review synthesizes data from peer-reviewed literature focusing on molecular oncology and rheumatology. The selection criteria prioritized studies elucidating specific signaling axes. In the context of TNBC, emphasis was placed on resistance mechanisms involving protein phosphatases, autophagy, and ferroptosis regulators. For OA, the search focused on synovial fluid biomarkers, macrophage polarization, and matrix degradation. Additionally, a specific subset of literature regarding plant-based interventions—specifically soybean bioactives—was analyzed to provide a translational perspective on therapeutic management. The synthesis of this data is qualitative, aiming to map overlapping signaling nodes such as the NF-kappaB pathway, Akt signaling, and oxidative stress responses across both disease states.

3. Results: Pathogenic Mechanisms and Therapeutic Targets

3.1 The Triple-Negative Breast Cancer Microenvironment

TNBC remains the most challenging breast cancer subtype to treat due to its heterogeneity and high rate of metastasis. Recent investigations have identified specific molecular drivers of this aggression. The stabilization of Stathmin 1 (STMN1) by Protein Phosphatase 1 Subunit PPP1R14B has been shown to promote progression and paclitaxel resistance, highlighting the critical role of cytoskeletal regulation in tumor survival [1]. Furthermore, the complexity of protein degradation pathways contributes significantly to cellular resilience. The TOLLIP-mediated autophagic degradation pathway, linking the VCP-TMEM63A-DERL1 signaling axis, represents a sophisticated mechanism by which TNBC cells manage proteotoxic stress to ensure survival [2].

A rapidly evolving area of interest is ferroptosis, an iron-dependent form of regulated cell death. Unlike apoptosis, ferroptosis is driven by the accumulation of lipid peroxides. In TNBC, ferroptosis heterogeneity reveals distinct metabolic vulnerabilities. Research indicates that hepatic leukemia factor (HLF) regulates ferroptosis and chemoresistance by activating crosstalk between tumor cells and macrophages [11]. This suggests that the tumor does not exist in isolation but actively recruits the immune system to shield itself from metabolic death. This heterogeneity also opens avenues for innovative combination strategies, where inducing ferroptosis could sensitize tumors to immunotherapy [3].

The immune landscape of TNBC is further complicated by the variable response to checkpoint inhibitors. Single-cell analyses have revealed key immune cell subsets associated with responses to PD-L1 blockade [5]. Clinical trials, such as IMpassion130 and GeparNuevo, have demonstrated that adding immune checkpoint inhibitors like atezolizumab or durvalumab to chemotherapy improves survival, although challenges remain in identifying the precise biomarkers for patient selection [6, 7, 8].

3.2 The Osteoarthritic Synovial Environment

Parallel to the TME in cancer, the synovial environment in OA acts as a reservoir for inflammatory signaling. The historical view of OA as solely a cartilage disease has been supplanted by evidence identifying inflammation as a relevant treatment target [16]. Synovial fibroblasts and macrophages drive the secretion of catabolic enzymes. Preliminary studies detecting Oligomeric Matrix Protein (COMP), TIMP-1, and MMP-3 in synovial fluid suggest these are potent indicators of disease progression [18]. Specifically, elevated MMP-3 gene expression in synovial fluid is a significant risk factor for knee osteoarthritis, correlating with the severity of joint destruction [19].

The driving force behind this enzymatic destruction is often the inflammatory activation of synovial fibroblasts. High mobility group box 1 (HMGB-1) has been shown to induce IL-6 production in human synovial fibroblasts through c-Src, Akt, and NF-kappaB pathways [22]. This signaling cascade bears a striking resemblance to the survival pathways activated in malignant cells, suggesting that the molecular machinery of "survival" in cancer is repurposed for "destruction" in chronic inflammation.

3.3 Bioactive Interventions: The Role of Soybean Peptides

Given the limitations of synthetic pharmacotherapy—toxicity in chemotherapy and cardiovascular risks in NSAIDs—natural bioactives offer an alternative. Soybean processing wastes and extracts have yielded novel insights into therapeutic properties [28]. Soybean saponins have been observed to suppress the release of proinflammatory mediators by LPS-stimulated peritoneal macrophages, effectively dampening the "cytokine storm" locally within tissues [25].

Furthermore, specific peptides such as the Bowman-Birk inhibitor have been shown to modify the transcription of autophagy and apoptosis genes [26]. In the context of bone and cartilage diseases, genistein (a soy isoflavone) exhibits protective activity, potentially countering the catabolic effects of inflammatory cytokines [27]. These findings position plant-based analogs not merely as nutritional substitutes but as sources of potent pharmacological agents capable of modulating the very pathways—autophagy, apoptosis, and inflammation—dysregulated in both TNBC and OA [23].

4. Comprehensive Analysis of Immunometabolic Crosstalk

4.1 Macrophage Polarization: The Central Axis of Pathology

To understand the connection between a metastatic breast tumor and a degenerating knee joint, one must look to the macrophage. These versatile immune cells possess remarkable plasticity, capable of shifting between a pro-inflammatory (M1-like) and an anti-inflammatory/pro-repair (M2-like) phenotype. However, in chronic disease, this plasticity is hijacked.

In the context of TNBC, macrophages are recruited to the tumor site and frequently polarized toward an M2-like phenotype (Tumor-Associated Macrophages, or TAMs). These TAMs suppress adaptive immunity, promote angiogenesis, and facilitate metastasis. The work by Li et al. (2022) demonstrates that HLF regulates ferroptosis and chemoresistance specifically by activating tumor cell-macrophage crosstalk [11]. This implies that the metabolic state of the cancer cell (its susceptibility to ferroptosis) dictates the behavior of the macrophage, and conversely, the macrophage provides survival signals that prevent ferroptosis. This is further supported by findings that chemotherapy coupled with macrophage inhibition induces T-cell and B-cell infiltration, leading to durable regression [12]. The macrophage, therefore, acts as a barrier to effective therapy.

Contrast this with Osteoarthritis. Here, the role of macrophage polarization is equally critical but functionally distinct. In OA and Rheumatoid Arthritis (RA), the synovial lining is infiltrated by macrophages that drive inflammation (often M1-dominant in acute flares, but mixed in chronic states). Chang and Tang (2024) emphasize the role of macrophage polarization in the pathogenesis of arthritis, noting that the persistence of inflammatory macrophages leads to the continuous production of MMPs and cytokines that erode cartilage [17]. Unlike TNBC, where the goal is often to *repolarize* macrophages to an M1 phenotype to attack the tumor, in OA, the goal is to dampen M1 activity or resolve the inflammation.

This dichotomy presents a fascinating pharmacological challenge. A therapy designed to treat TNBC might aim to induce oxidative stress and M1 activation, whereas a therapy for OA aims to reduce oxidative stress and suppress M1 activation. However, natural immunomodulators like soy saponins appear to act as "regulators" rather than simple accelerators or brakes. By suppressing LPS-stimulated mediators [25], they prevent the extreme inflammatory spikes that drive tissue damage in OA,

while potentially normalizing the immune microenvironment in cancer to allow for better surveillance.

4.2 Ferroptosis: Metabolic Vulnerability and Tissue Preservation

The concept of ferroptosis provides a lens through which to view the metabolic divergence of these diseases. Ferroptosis is characterized by the iron-dependent accumulation of lipid reactive oxygen species (ROS).

In TNBC, the induction of ferroptosis is a desirable therapeutic goal. Cancer cells, due to their high metabolic rate, are often under significant oxidative stress and rely heavily on antioxidant defense systems (like the system Xc- cystine/glutamate antiporter) to survive. Strategies that inhibit these defenses trigger ferroptosis. The heterogeneity of ferroptosis sensitivity in TNBC [3] suggests that some tumors have evolved robust mechanisms to sequester iron or detoxify lipids. The RGS5(+) lymphatic endothelial cells described by Qiu et al. (2024) facilitate metastasis and drug resistance through an oxidative stress-sensing mechanism, essentially protecting the tumor from oxidative death [4].

Conversely, in OA, ferroptosis is a pathological driver of tissue loss. Chondrocytes (cartilage cells) are quiescent and struggle to repair damage. The accumulation of iron and lipid peroxides in the joint space triggers chondrocyte ferroptosis, leading to cartilage loss. Therefore, in OA, the therapeutic goal is to *inhibit* ferroptosis. This creates a complex landscape for drug development. However, it underscores the importance of targeted delivery.

Interestingly, the DNA methylation landscape of tumor-associated macrophages reveals pathways relevant to patient prognosis [10]. Epigenetic modifications may dictate whether a macrophage supports ferroptosis (in cancer defense) or suppresses it (in cancer promotion). Understanding these epigenetic switches is crucial for developing "smart" therapies that can distinguish between the context of a tumor and a degenerating joint.

4.3 The VCAM-1 and Cytokine Connection

The signaling pathways converge further on adhesion molecules and cytokines. In inflammatory arthritis, VCAM-1-dependent monocyte adhesion is a key step in immune cell infiltration into the synovium. Antcin K has been shown to inhibit this adhesion in synovial fibroblasts [21]. Similarly, in the tumor microenvironment, adhesion molecules regulate the recruitment of immune cells. The HMGB-1/IL-6 axis identified in synovial fibroblasts [22] is almost identical to pathways seen in the TME, where IL-6 is a known promoter of cancer stemness and resistance.

The presence of microRNAs, such as miR-21b and miR-146a, which discriminate arthritis severity [15], suggests that post-transcriptional regulation controls this cytokine output. It is highly probable that similar miRNA dysregulation underpins the TOLLIP-mediated autophagy seen in TNBC [2]. If common miRNA signatures exist, they could serve as universal biomarkers for "chronic inflammatory stress," regardless of whether the tissue outcome is neoplasia or degeneration.

4.4 Nutritional Biochemistry as a Modulatory Tool

The discussion of therapeutic interventions must include the significant potential of plant-based biochemistry. The analysis of soy bioactive peptides [24] and their functional properties reveals a capacity to interact with mammalian cell signaling. The observation that Bowman-Birk inhibitors modify autophagy and apoptosis genes [26] is particularly relevant. Autophagy is a survival mechanism for TNBC cells (via TOLLIP) [2]. If soy peptides can modulate autophagy, they could theoretically sensitize cancer cells to chemotherapy.

Simultaneously, in the context of OA, the protective activity of genistein against bone and cartilage disease [27] relies on its estrogen-like (phytoestrogen) properties and its antioxidant capacity. By neutralizing ROS, genistein prevents the lipid peroxidation that leads to chondrocyte ferroptosis. Thus, a single compound could potentially offer dual benefits: inhibiting the pro-survival autophagy in cancer cells while preventing the pro-death ferroptosis in healthy chondrocytes, largely due to the differential signaling baselines of these cell types.

Furthermore, the formulation of these bioactives matters. The structural and textural properties of plant-based analogues [23] influence bioavailability. As we look toward procedural treatments for OA, such as injectable therapies [20], the incorporation of concentrated bioactive peptides into hydrogels or intra-articular injections represents a frontier in regenerative medicine.

4.5 Challenges in Immunotherapy and Future Directions

Despite the promise of these mechanisms, clinical application remains fraught with challenges. In TNBC, while atezolizumab plus nab-paclitaxel improves progression-free survival [6], not all patients respond. The progress and challenges of immunotherapy [9] are linked to the "cold" nature of some TNBC tumors—those with poor immune infiltration. Strategies that couple chemotherapy with macrophage inhibition to induce T-cell infiltration [12] are attempting to turn "cold" tumors "hot."

Future research must focus on the integration of these disciplines. Can the ferroptosis-inducing agents developed for oncology be modified to spare chondrocytes? Can the anti-

inflammatory strategies of rheumatology (like IL-6 blockade) be more effectively deployed in cancer to reduce metastatic niche formation? The data suggests that the boundary between "oncology" and "rheumatology" is becoming increasingly blurred at the molecular level.

5. Conclusion

The pathogenesis of Triple-Negative Breast Cancer and Osteoarthritis, though manifesting in vastly different clinical phenotypes, is underpinned by a shared infrastructure of dysregulated inflammation. The central protagonist in both narratives is the macrophage, whose polarization status determines whether tissue is repaired, destroyed, or co-opted for malignant growth. The molecular machinery of ferroptosis, autophagy, and the VCP-TMEM63A-DERL1 axis highlights the metabolic vulnerabilities inherent in these disease states.

The comprehensive analysis of literature reveals that therapeutic success lies in mastering this immunometabolic crosstalk. Current chemotherapeutic and immunotherapeutic approaches in TNBC are potent but limited by resistance mechanisms often driven by the microenvironment. Similarly, OA treatments are frequently palliative rather than disease-modifying. The integration of bioactive compounds, particularly soybean-derived peptides and saponins, offers a compelling comprehensive approach. These agents demonstrate the unique capacity to modulate inflammation and autophagy in a context-dependent manner.

Ultimately, the future of treatment for these chronic pathologies may not lie in ever-more specific cytotoxicity, but in the broad renormalization of the tissue microenvironment. By targeting the shared pathways of oxidative stress and macrophage dysfunction, we may develop therapeutic paradigms that are effective across the spectrum of chronic human disease.

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Part 4: Final Assembly & Formatting

Immunometabolic Landscapes of Chronic Pathology: A Comparative Review of Macrophage Plasticity, Ferroptosis, and Therapeutic Interventions in Triple-Negative Breast Cancer and Osteoarthritis

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Abstract

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Methods: This review synthesizes recent literature to map the molecular intersections between TNBC progression and OA pathogenesis. We analyzed mechanisms of chemoresistance in TNBC, specifically focusing on the VCP-TMEM63A-DERL1 axis and ferroptosis, and contrasted these with synovial inflammation and matrix metalloproteinase (MMP) activity in OA. Furthermore, we evaluated the therapeutic efficacy of soybean-derived bioactive peptides and saponins across these conditions.

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Conclusion: There is a remarkable convergence in the signaling nodes governing TNBC and OA. Targeting the inflammatory microenvironment through metabolic modulation—specifically via ferroptosis induction in cancer and inflammatory suppression in arthritis—offers a promising therapeutic avenue. Natural bioactive compounds warrant further investigation as potent, pleiotropic agents capable of addressing these shared molecular targets.

Keywords: Triple-Negative Breast Cancer, Osteoarthritis, Macrophage Polarization, Ferroptosis, Soybean Bioactives, Inflammation, Immunotherapy.

1. Introduction

The global burden of disease has shifted dramatically in recent decades, characterized by a dual rise in aggressive malignancies and chronic degenerative conditions. According to systematic analyses for the Global Burden of Disease Study, these pathologies account for a significant proportion of disability-adjusted life years worldwide [13]. Among these, Triple-Negative Breast Cancer (TNBC) stands out as a clinical entity defined by its lack of estrogen, progesterone, and HER2 receptors, rendering it unresponsive to conventional hormonal therapies and particularly reliant on cytotoxic chemotherapy and emerging immunotherapies [6]. Concurrently, Osteoarthritis (OA), once viewed merely as "wear and tear" of the cartilage, is now understood as a complex, whole-joint disease driven by low-grade, chronic inflammation, with the synovium playing a pivotal role in pathogenesis [14].

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Contrast this with Osteoarthritis. Here, the role of macrophage polarization is equally critical but functionally distinct. In OA and Rheumatoid Arthritis (RA), the synovial lining is infiltrated by macrophages that drive inflammation (often M1-dominant in acute flares, but mixed in chronic states). Chang and Tang (2024) emphasize the role of macrophage polarization in the pathogenesis of arthritis, noting that the persistence of inflammatory macrophages leads to the continuous production of MMPs and cytokines that erode cartilage [17]. Unlike TNBC, where the goal is often to *repolarize* macrophages to an M1 phenotype to attack the tumor, in OA, the goal is to dampen M1 activity or resolve the inflammation.

This dichotomy presents a fascinating pharmacological challenge. A therapy designed to treat TNBC might aim to induce oxidative stress and M1 activation, whereas a therapy for OA

aims to reduce oxidative stress and suppress M1 activation. However, natural immunomodulators like soy saponins appear to act as "regulators" rather than simple accelerators or brakes. By suppressing LPS-stimulated mediators [25], they prevent the extreme inflammatory spikes that drive tissue damage in OA, while potentially normalizing the immune microenvironment in cancer to allow for better surveillance.

4.2 Ferroptosis: Metabolic Vulnerability and Tissue Preservation

The concept of ferroptosis provides a lens through which to view the metabolic divergence of these diseases. Ferroptosis is characterized by the iron-dependent accumulation of lipid reactive oxygen species (ROS).

In TNBC, the induction of ferroptosis is a desirable therapeutic goal. Cancer cells, due to their high metabolic rate, are often under significant oxidative stress and rely heavily on antioxidant defense systems (like the system Xc- cystine/glutamate antiporter) to survive. Strategies that inhibit these defenses trigger ferroptosis. The heterogeneity of ferroptosis sensitivity in TNBC [3] suggests that some tumors have evolved robust mechanisms to sequester iron or detoxify lipids. The RGS5(+) lymphatic endothelial cells described by Qiu et al. (2024) facilitate metastasis and drug resistance through an oxidative stress-sensing mechanism, essentially protecting the tumor from oxidative death [4].

Conversely, in OA, ferroptosis is a pathological driver of tissue loss. Chondrocytes (cartilage cells) are quiescent and struggle to repair damage. The accumulation of iron and lipid peroxides in the joint space triggers chondrocyte ferroptosis, leading to cartilage loss. Therefore, in OA, the therapeutic goal is to *inhibit* ferroptosis. This creates a complex landscape for drug development. However, it underscores the importance of targeted delivery.

Interestingly, the DNA methylation landscape of tumor-associated macrophages reveals pathways relevant to patient prognosis [10]. Epigenetic modifications may dictate whether a macrophage supports ferroptosis (in cancer defense) or suppresses it (in cancer promotion). Understanding these epigenetic switches is crucial for developing "smart" therapies that can distinguish between the context of a tumor and a degenerating joint.

4.3 The VCAM-1 and Cytokine Connection

The signaling pathways converge further on adhesion molecules and cytokines. In inflammatory arthritis, VCAM-1-dependent monocyte adhesion is a key step in immune cell infiltration into the synovium. Antcin K has been shown to inhibit this adhesion in synovial fibroblasts [21]. Similarly, in the tumor microenvironment, adhesion molecules regulate the recruitment of immune cells. The HMGB-1/IL-6 axis identified in synovial fibroblasts [22] is almost identical to pathways seen in the TME, where IL-6 is a known promoter of cancer stemness and resistance.

The presence of microRNAs, such as miR-21b and miR-146a, which discriminate arthritis severity [15], suggests that post-transcriptional regulation controls this cytokine output. It is highly probable that similar miRNA dysregulation underpins the TOLLIP-mediated autophagy seen in TNBC [2]. If common miRNA signatures exist, they could serve as universal biomarkers for "chronic inflammatory stress," regardless of whether the tissue outcome is neoplasia or degeneration.

4.4 Nutritional Biochemistry as a Modulatory Tool

The discussion of therapeutic interventions must include the significant potential of plant-based biochemistry. The analysis of soy bioactive peptides [24] and their functional properties reveals a capacity to interact with mammalian cell signaling. The observation that Bowman-Birk inhibitors modify autophagy and apoptosis genes [26] is particularly relevant. Autophagy is a survival mechanism for TNBC cells (via TOLLIP) [2]. If soy peptides can modulate autophagy, they could theoretically sensitize cancer cells to chemotherapy.

Simultaneously, in the context of OA, the protective activity of genistein against bone and cartilage disease [27] relies on its estrogen-like (phytoestrogen) properties and its antioxidant capacity. By neutralizing ROS, genistein prevents the lipid peroxidation that leads to chondrocyte ferroptosis. Thus, a single compound could potentially offer dual benefits: inhibiting the pro-survival autophagy in cancer cells while preventing the pro-death ferroptosis in healthy chondrocytes, largely due to the differential signaling baselines of these cell types.

Furthermore, the formulation of these bioactives matters. The structural and textural properties of plant-based analogues [23] influence bioavailability. As we look toward procedural treatments for OA, such as injectable therapies [20], the incorporation of concentrated bioactive peptides into hydrogels or intra-articular injections represents a frontier in regenerative medicine.

4.5 Challenges in Immunotherapy and Future Directions

Despite the promise of these mechanisms, clinical application remains fraught with challenges. In TNBC, while atezolizumab plus nab-paclitaxel improves progression-free survival [6], not all patients respond. The progress and challenges of immunotherapy [9] are linked to the "cold" nature of some TNBC tumors—those with poor immune infiltration. Strategies

that couple chemotherapy with macrophage inhibition to induce T-cell infiltration [12] are attempting to turn "cold" tumors "hot."

Future research must focus on the integration of these disciplines. Can the ferroptosis-inducing agents developed for oncology be modified to spare chondrocytes? Can the anti-inflammatory strategies of rheumatology (like IL-6 blockade) be more effectively deployed in cancer to reduce metastatic niche formation? The data suggests that the boundary between "oncology" and "rheumatology" is becoming increasingly blurred at the molecular level.

5. Conclusion

The pathogenesis of Triple-Negative Breast Cancer and Osteoarthritis, though manifesting in vastly different clinical phenotypes, is underpinned by a shared infrastructure of dysregulated inflammation. The central protagonist in both narratives is the macrophage, whose polarization status determines whether tissue is repaired, destroyed, or co-opted for malignant growth. The molecular machinery of ferroptosis, autophagy, and the VCP-TMEM63A-DERL1 axis highlights the metabolic vulnerabilities inherent in these disease states.

The comprehensive analysis of literature reveals that therapeutic success lies in mastering this immunometabolic crosstalk. Current chemotherapeutic and immunotherapeutic approaches in TNBC are potent but limited by resistance mechanisms often driven by the microenvironment. Similarly, OA treatments are frequently palliative rather than disease-modifying. The integration of bioactive compounds, particularly soybean-derived peptides and saponins, offers a compelling comprehensive approach. These agents demonstrate the unique capacity to modulate inflammation and autophagy in a context-dependent manner.

Ultimately, the future of treatment for these chronic pathologies may not lie in ever-more specific cytotoxicity, but in the broad renormalization of the tissue microenvironment. By targeting the shared pathways of oxidative stress and macrophage dysfunction, we may develop therapeutic paradigms that are effective across the spectrum of chronic human disease.

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