Centrosome in Inflammatory Response/Metastatic Process

Subjects: Biology

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The centrosome plays a major role in organizing the microtubule cytoskeleton in animal cells regulating cellular architecture and cell division. Loss of centrosome integrity activates the p38-p53-p21 pathway, which results in cell-cycle arrest or senescence and acts as a cell-cycle checkpoint pathway. Structural and numerical centrosome abnormalities can lead to aneuploidy and chromosomal instability (CIN). New findings derived from studies on cancer and rare genetic disorders suggest that centrosome dysfunction alters the cellular microenvironment through Rho GTPases, p38, and JNK (c-Jun N-terminal Kinase)-dependent signaling in a way that is favorable for pro-invasive secretory phenotypes and aneuploidy tolerance.

centrosome chromosome instability Rho GTPases p38 MAPK tumor microenvironment

1. Introduction

The overwhelming majority of cancer mortality is caused by metastasis, a complex process that remains the least understood aspect of cancer biology [1]. Metastasis is a process in which cancer cells disseminate from the primary tumor and seed new colonies at distant sites. It involves the local invasion of primary-tumor cells into surrounding tissue, intravasation of these cells into the circulatory system, and subsequent extravasation to other tissues through the vascular walls [1].

In this way, cancer cells travel to the parenchyma of a distant tissue and seed microscopic colonies that proliferate to form metastatic lesions. In addition to cancer cell-autonomous mechanisms, metastatic growth depends on the interactions of cancer cells with their niche microenvironment and the crosstalk with various stromal cells, including endothelial cells, fibroblasts, and cells from the innate and adaptive immune system [2]. Over the last years, the biological programs that underlie the dissemination and metastatic outgrowth of cancer cells have begun to emerge. An important aspect is the diversification and adaptation of cancer cells that can be achieved by two main biological processes (1) the dormancy programs (DP) characterized by the activation of quiescence and survival pathways and (2) epithelial-mesenchymal transition (EMT) in which epithelial cells lose their cell polarity and cell-cell adhesions, and gain migratory and invasive properties to become under certain conditions mesenchymal cells that sometimes present stem cell-like properties [2][3]. Notably, in addition to phenotypic differences, significant genotypic diversity exists within tumors, a process known as intra-tumor heterogeneity (ITH) that can be observed at the genetic, proteomic, morphological, and environmental level [4].

One of the central drivers of intra-tumor diversification is the chromosome copy number, instability of particular loci, large chromosome segments, or entire chromosomes. This instability may alter the chromosomal content of a cell (aneuploidy). Karyotypic heterogeneity in tumor cells derives from “chromosomal instability” (CIN), a hallmark that not only generates abnormal aneuploid karyotypes, but also expands continually phenotypic heterogeneity as tumor cell populations undergo consecutive cell divisions [5].

2. Aneuploidy and CIN: Two Sides to the Debate in Cancer

The link between chromosomal abnormalities and cancer was first proposed by the German biologist, Theodor Boveri, over a hundred years ago [6]. Decades of studies have shown that errors in mechanisms of cell division are an important source of genomic diversification that promotes ITH and cancer evolution. Paradoxically, despite the observation that aneuploidy is an unfavorable state for cancer cells, most healthy cells such as osteoclasts or hepatocytes are highly aneuploid [6]. Therefore, aneuploidy is increasingly recognized as a factor that might promote genetic diversity. Aneuploidy is present in around 80% of human solid neoplasms [7].

Cytokinesis failure leads to both centrosome amplification and production of tetraploid cells, which may set the stage for the development of tumor cells (Figure 1A,B). However, tetraploid cells are abundant components at the organism and sub-organism levels in normal tissues, including the liver and heart, indicating that polyploid cellular processes are physiologically relevant and required in generating biodiversity and biocomplexity [8]. The reason why tetraploidy is both beneficial and detrimental for cellular fitness, depending on the cellular context, remains unknown. Other errors in chromosome segregation during mitosis that can lead to karyotype heterogeneity include the formation of micronuclei (Figure 1A,B).

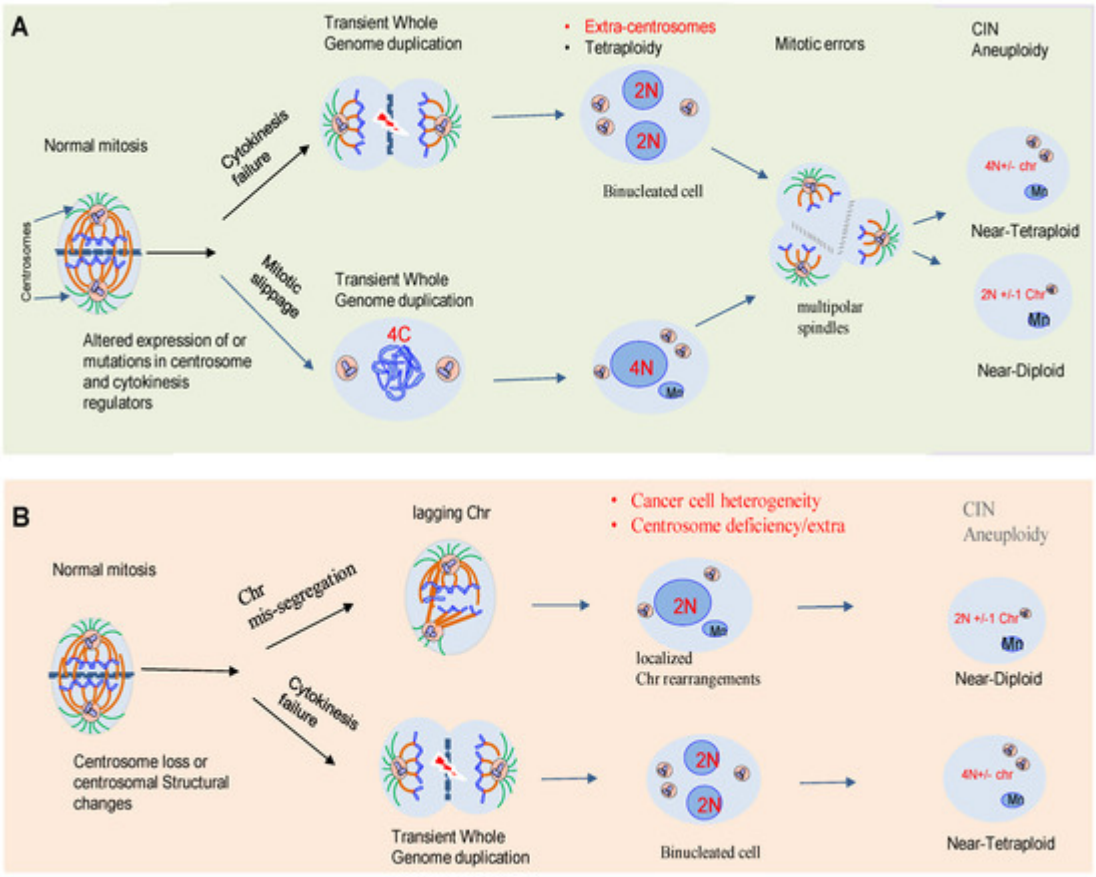

Figure 1. The route to aneuploidy and its link to centrosome dysfunction. (**A**) Aneuploidy is caused by errors in chromosome partitioning during mitosis. Changes include whole chromosomes (numerical aneuploidy) often caused by altered expression or mutations in centrosome (i.e., CEP55) and cytokinesis (i.e., PRC1) regulators [6]. (**B**) Centrosome loss or structural changes in its components are early drivers of genomic instability causing both localized chromosome rearrangements and transient tetraploidy [9]. These alterations will generate intra-tumor heterogeneity and tumors containing a mix of cells with extra-numerical centrosomes or loss of its components. In general, little is known about the mechanisms of centrosome loss. However, centrosomes are normally inactivated or lost during specific developmental stages in different animals. Abbreviations: Chromosome, Chr; CIN; Chromosome instability.

3. Centrosome Biology and CIN

In animal cells, the centrosome is the major microtubule-organizing center (MTOC) [6]. The core of the centrosome consists of centrioles of nine microtubule (MT) triplets embedded in an ordered and protein-rich matrix called pericentriolar material (PCM). Centrosomes promote the production of bipolar mitotic spindles and supply a matrix of primary cilia in various cell types (Figure 2A) [10][11]. In addition to these structural functions, centrosomes and primary cilia have also evolved into essential signaling hubs to build and regulate the sensory/motor characters of metazoans [12][13]. It is increasingly recognized that centrosome is an organizing unit not only for MTs, but also for actin, Golgi apparatus, and signaling molecules coordinating cell migration, cell polarity, and fundamental signal transduction pathways [14][15]. Large-scale proteomic studies have revealed that there are more than 400

centrosome-associated proteins (about 3% of human proteome, but the exact functions of most of these proteins are still unknown and require further investigation. However, recent advances in imaging, proteomics, and structural biology have revealed new insights into how microtubule-associated proteins regulate the structure, length, and stability of centrosome/cilium complex opening up new avenues for future research [6][15][16][17].

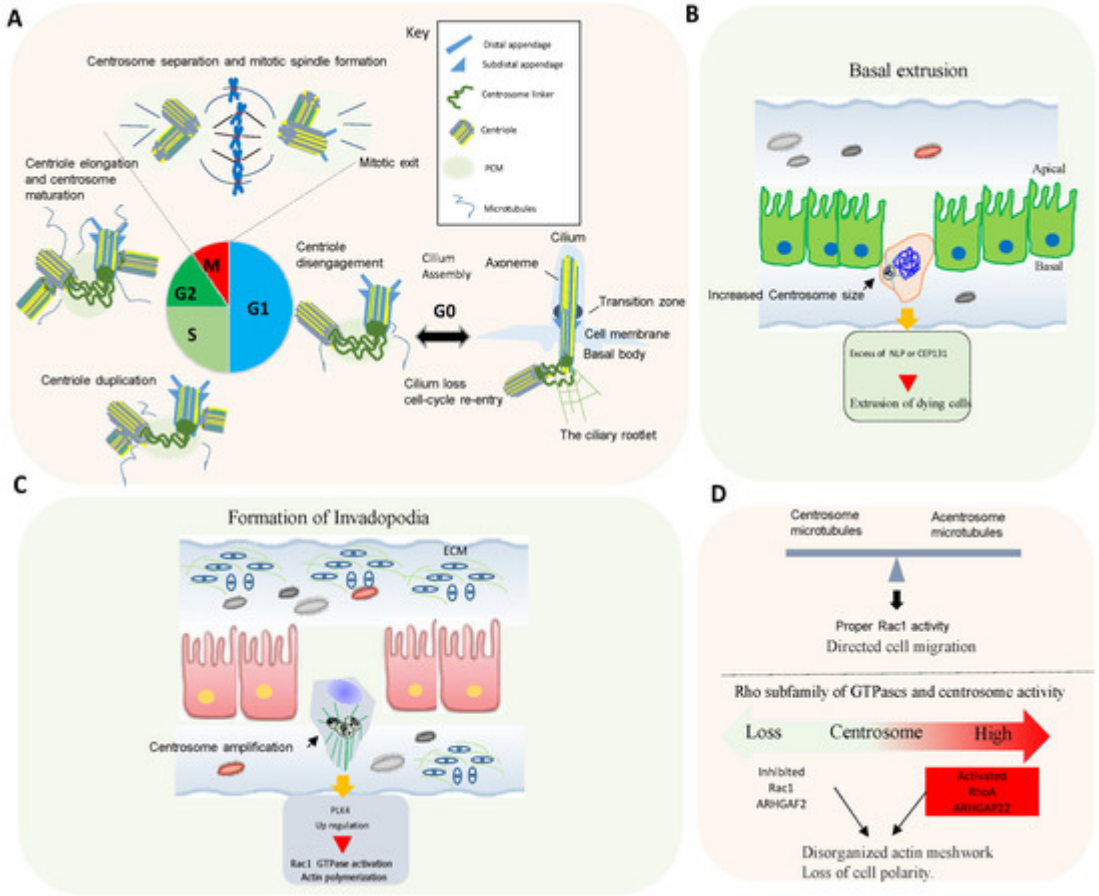

Figure 2. Centrosome cycle and its role in cell motility and invasion. (**A**) In dividing cells, the centrosome duplicates once per cell cycle and segregates in concert with cell-division cycle. The centrosome number and structure are highly regulated during each cell cycle to organize an effective bipolar spindle in the mitotic phase. At the end of mitosis, the daughter centriole disengages from the mother centriole and a centrosome linker is established. When cells enter G0 phase, centrioles can become basal bodies that organize the primary cilium. Shared pathways ensure the coordination between centrosome dynamics, chromosome replication–segregation cycles, and ciliogenesis. Details on the centrosome/cilia dynamins can be found in recent excellent reviews [6][10][12][15][16]. (**B**) Excess of expression of centrosome genes (structural changes) can disrupt apical cell extrusion, instead, causing aberrant basal extrusion. (**C**) Centrosome amplification triggered by overexpression of Plk4 induces the formation of invasive protrusions (invadopodia), which are accompanied by the degradation of ECM components. The increase in centrosomal microtubule nucleation in cells with extra centrosomes promotes activation of the small GTPase Rac1. Rac1 activity, in turn, initiates actin polymerization that disrupt cell-cell adhesion and promotes cell migration. (**D**) Up, the centrosome acts as a controller and balances the formation of centrosomal and acentrosomal microtubules. The presence of centrosome regulates proper Rac1 activity and allows directed cell migration. Down, centrosome activity (loss or activation) regulates differently members of Rho

family of GTPases family. Interference or an excess with the formation of centrosome increases acentrosome, microtubules assembly, and activation of Rac1, which in turn leads to the loss of cell polarity.

4. Rho GTPases Signaling and Centrosome Aberrations

Proteins controlling microtubule dynamics and processes that require changes in cell shape and motility are important for tumor dissemination. Rho GTPase signaling is commonly altered in human tumors, and an elevated expression and/or activation of Rho GTPases often correlates with tumor progression, metastasis, and poor prognosis [18].

Centrosome disruption induces excessive Rac1 activation around the cell periphery, causing rapid focal adhesion turnover, a disorganized actin network, randomly protruding lamellipodia, and the loss of cell polarity [19]. This supports that the centrosome integrity guides the spatial activation of Rac1 to control normal cell polarization and directed cell migration (Figure 2D).

Conversely, centrosome amplification in cultured cells also activates Rac1. In fact, in cells with extra centrosomes, increased centrosomal microtubule nucleation leads to Rac1 activation, disruption of cell-cell contacts, and invasive behavior [6][18].

5. Centrosome, Cell Cycle and Inflammatory Responses

In spite of its connection to aggressiveness, it remains to be fully understood the precise contribution of chromosomal instability to cancer phenotypes. Recent reports have shown that genomic instability and DNA damage leads to DNA and cGAS–STING-induced inflammation signaling, which affects cellular antigen presentation [7][20]. These pathways are often triggered by non-canonical NF-kB (Nuclear factor-κB) signaling, as well as coopting myeloid cell mobility programs. Centrosome aberrations (numerical or structural) can be associated with additional factors such as age, inflammation, hypoxia, other environmental influences, or a combination of circumstances. Cells have evolved mechanisms to generate several inflammatory response systems to tackle DNA and centrosome lesions in order to maintain their genome integrity [21]. For example, pro-inflammatory signals through IKKα (Inhibitor of NF-kB kinase α) activation induce nucleophosmin (NPM) hexamer formation, which in turn, leads to the association of NPM with centrosomes in M phase in the case of human cells or in the M phase and interphase in mouse cells. Consistently, loss of IKKα or NPM, decreases the levels of NPM hexamers and its association with centrosomes, thereby promoting centrosome amplification (Figure 3A) [22]. Although IKKα-NPM axis may suppress tumor progression through maintaining proper centrosome duplication in a pro-inflammatory microenvironment, the underlying molecular mechanisms on the interplay between IKKα-NPM axis and centrosomes deserve future investigations.

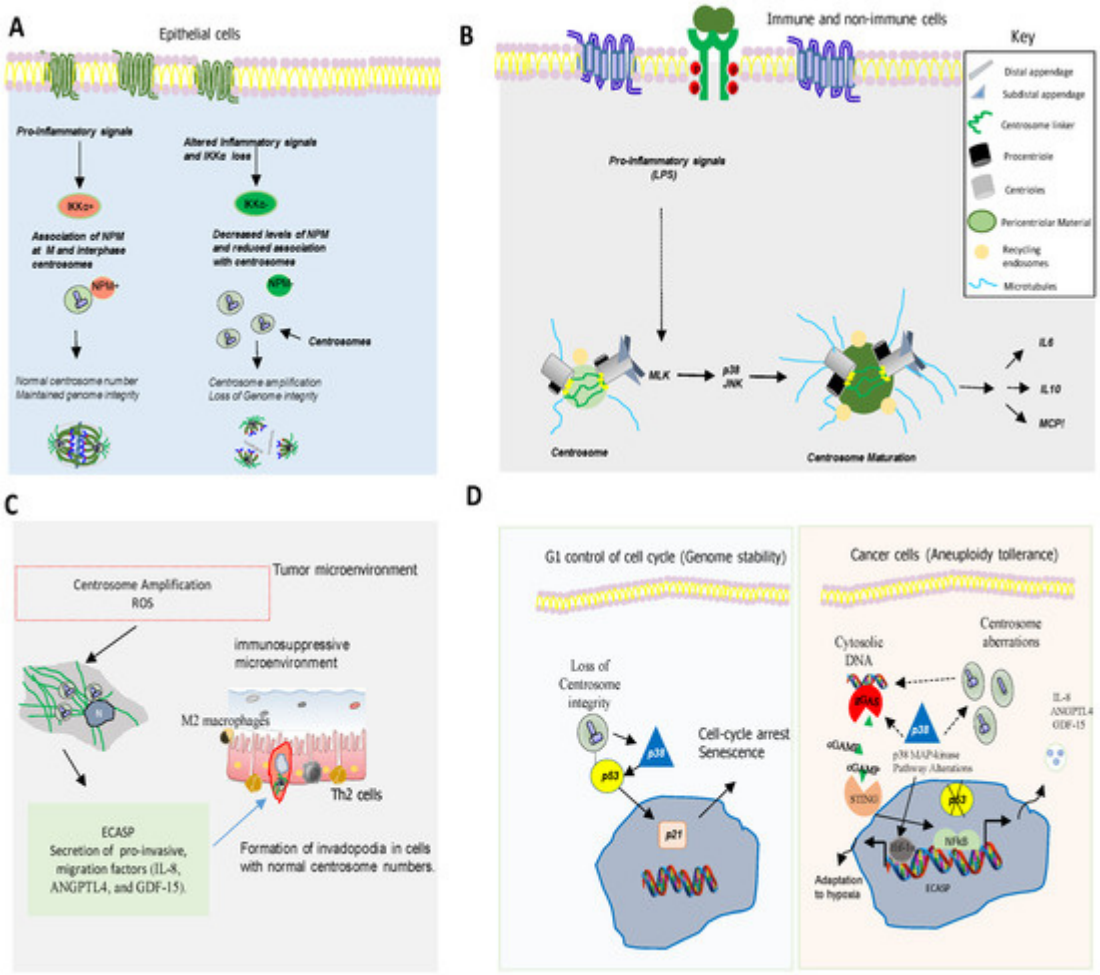

Figure 3. Chromosome instability in cancer and inflammatory responses. (**A**) Pro-inflammatory cytokines activate the IKKα/Nucleophosmin (NPM) hexamer formation and centrosome interplay in mouse and human cells [22]. IKKα activation and increased NPM levels (red) allow NPM-Centrosome interaction, which allows the maintenance of normal centrosome number and genome integrity. Right, IKKα or NPM loss (green), decreases the levels of NPM hexamers and the association of NPM with centrosomes, thereby promoting centrosome amplification and genome changes that predispose to cancer [22]. (**B**) Exposure to LPS induces the axis MLK-p38-JNK which is critical for interphase centrosome maturation and secretion of inflammatory cytokines by immune and non-immune cells. (**C**) Centrosome amplification facilitates the release of proinvasive factors (ECASP) to induce non-cell-autonomous invasion. Although it remains undetermined how the additional centrosomes promote the ECASP, it is dependent on elevated levels of reactive oxygen species in cells with amplified centrosomes. The release of proinvasive factors is required for invadopodia formation in cells with normal centrosomes. Chronic NF-κB activation mediates the ECASP through the regulation of proteins, including IL-8, to shape the immunosuppressive microenvironment. (**D**) Loss of centrosome integrity activates p38-p53-p21 pathway resulting in cell-cycle arrest or senescence acting as a cell-cycle checkpoint pathway. In cancer cells, centrosome dysfunction leads to the generation of cytosolic dsDNA, which in turn, activates the cGAS–STING and alternative inflammatory pathways such as NF-κB signaling leading to ECASP. Centrosome abnormalities in cooperation with p38 and p53 dysfunction can also lead aneuploidy tolerance and adaptation to hypoxia.

Nevertheless, centrosome polarization is required for full activation of T lymphocytes, including the generation and secretion of cytokines highlighting the relevance of centrosome translocation [6]. In fact, centrosome maturation, expansion of PCM that occurs as cells pass through specific phases, is essential for the secretion of a number of cytokines such as IL-6 (Interleukin 6), IL-10, and MCP1 (Monocyte chemoattractant protein-1), but not TNF-α (Tumor necrosis factor-α) [23]. Pro-inflammatory stimuli activate interphase centrosome maturation in both immune and non-immune cells through a mechanism dependent on MLK (mixed-lineage kinase) and p38 or JNK (Figure 3B). More recent observations support a model in which supernumerary centrosomes in cancer cells can promote the overproduction and secretion of cytokines and pro-invasive factors, such as IL-8, ANGPTL4 (Angiopoietin Like 4), and GDF-15 (Growth Differentiation Factor 15). Notably, conditioned media from cells with extra centrosomes induce the formation of invasive protrusions in 3D cell organoid cultures with a normal number of centrosomes independently of Rac1, a phenomenon called non-cell-autonomous extra centrosomes-associated secretory pathway (ECASP) [24]. (Figure 3C). Other convincing evidence for the link between centrosome biology and inflammation comes from the observation that cells from patients that have a mutant pericentrin gene are susceptible to infections and their immune response is defective [23]. It is also remarkable that patients with human hereditary disorders carrying mutant centrosomal genes *ALMS1* (Alstrom Syndrome) and *CEP250* (Retinitis Pigmentosa) show a severe deficit in the immune response, inflammation, and extracellular matrix (ECM)-cell interactions [25][26]. In this context, p38 MAPK kinase plays a key role balancing centrosome dynamics regulation with cell cycle and inflammatory responses, for example, controlling mitotic entry timing [27]. Notably, loss of centrosome integrity activates p38 MAPK leading to a p38-p53-p21-dependent G1-S arrest, highlighting the important role played by p38 in maintaining chromosome stability and an attenuated inflammatory response [28] (Figure 3D). The centrosome defects that activate p38 have also been involved in the induction of cellular senescence. This is an irreversible type of growth arrest that is produced in cleavable cells that suffer extensive intrinsic and/or extrinsic damage which connects aging and cancer affecting also immunity [27][28].

At late stages of viral infection, p38-mediated phosphorylation of USP21 (Ubiquitin Specific Peptidase 21), a deubiquitinating enzyme, inhibits STING. p38 pathway appears to be also active in tumor cells with unstable chromosomes in response to the stress induced by chromosome missegregation and endogenous DNA damage [7]. Interestingly, pharmacologic inhibition of p38, selectively regulates type I interferon signaling downstream of STING, whereas other STING-related pathways are not affected (Figure 3D). Therefore, the effects of cGAS-STING activation in cancer depend on the context, being mainly affected by the ongoing aneuploidy state and the level of activity of p38 MAPK.

6. p38MAPK as a Key Mediator of Chromosome Stability and Cell Cycle

One of the main causes of CIN is the deregulation of the cell cycle [29]. p38MAPK regulates cell cycle in different situations, controlling genomic instability. For example, p38MAPK controls cell cycle at G0, G1/S, and G2/M transitions to ensure genetic integrity and stability of the cell at each step [29]. p38MAPK also regulates actin cytoskeleton organization, which is required for cytokinesis and mitosis [30][31]. Hence, p38α MAPK deficiency in

hepatocytes induces actin disassembly and cytokinesis failure, which leads to the generation of genetically unstable polyploid cells [31]. Furthermore, inhibition of p38MAPK in combination with taxanes increases genomic instability and DNA damage, impairing DNA replication in breast cancer cells [32].

Several observations indicate that p38MAPK, a kinase activated by various types of stress [33][34] also plays a pivotal role in chromosome mis-segregation and aneuploidy tolerance upstream of p53 [35][36][37] (Figure 3D). This is supported by studies showing that pharmacological chemical inhibition of p38MAPK overcomes p53-dependent cell-cycle arrest after prolonged mitosis or chromosome mis-segregation [38][39] and enhances CIN [40]. It is known that activation of p38MAPK in response to DNA damage induces a G2/M cell cycle checkpoint to repair DNA through p53-dependent mechanisms [38][39][40] (Figure 3D).

Centrosome abnormalities are additional causes of CIN and p38MAPK has emerged as a kinase with a key role in centrosome dysfunction. Hence, the inhibition of p38MAPK rescued cell cycle progression after depletion of centrosome proteins [41]. Evidence also shows that p38MAPK activity is essential for centrosome normal functioning. For example, p38MAPK localizes at the mitotic centrosome allowing chromosomal segregation [41]. Furthermore, localization of p38α MAPK at the kinetochores and the centrosome is also essential for proper chromosomal segregation [42][41]. Active p38MAPK has also been localized at other structures such as the centriolar satellites, discovering a p38MAPK/MK2/14-3-3 signaling cascade that targets centrosome functions and modulates its response to cell stress [41]. All this evidence point to p38MAPK as a key component of a feedback pathway quality control that operates in mitosis and cell division to detect and transform chromosome alterations into a robust G1 arrest, often dependent on p53.

7. p38MAPKs in Aneuploidy, Inflammation and Immune Evasion

it is important to underline the relevant role of p38 MAPKs regulating the expression of pro-inflammatory molecules. p38α MAPK is involved in the induction of the expression of several inflammatory cytokines [43] such as TNF-α, IL-1, and IL-6 and other mediators of inflammation such as cyclooxygenase 2 (COX2), contributing to the development and progression of gliomas, breast cancer, head and neck squamous cell carcinoma, skin cancer or colorectal cancer (CRC) [44][45][46][47]. The regulation of these pro-inflammatory molecules by p38α pathway includes transcriptional and posttranscriptional mechanisms [47][48][49][50]. MK2, a p38α downstream kinase, plays a key role in this posttranscriptional regulation by stabilizing mRNAs and promoting translation [46]. For example, MK2 increases interleukin IL-6 expression through stabilization of its mRNA, while TNF-α production is enhanced by promoting its translation [48]. RNA binding proteins (RBDs), such as AUF-1, HuR (Human antigen R), and TTP (tristetraprolin) interact with mRNAs AU-rich sequences in the 3'Unstranslated region (UTR) to regulate their stability and MK2 controls the activity of these proteins [48]. In particular, TTP promotes mRNAs degradation, action inhibited by p38 and/or MK2 [51][52][53], for example, to increase TNF-α mRNA stability [54][55] and other mRNAs involved in inflammation and cancer growth such as COX-2 (Cyclooxygenase-2), VEGF (Vascular endothelial growth factor), and IL-10 [2].

8. Conclusions and Future Perspective

The existing evidence suggests that centrosomes play a key role in the regulation of cell senescence, an irreversible type of growth arrest that takes place when cells suffer extensive intrinsic and/or extrinsic damage. Centrosome dysfunction is inseparably linked to aneuploidy and CIN, both hallmarks of tumor cells. Recent advances indicate that centrosome defects (numerical and structural) could contribute to accelerate cancer cell immune evasion through different mechanisms. The inflammatory microenvironment could also result in aneuploidy and spread CIN in tumor cells by inducing a direct genotoxic stress and/or an epithelial–mesenchymal transition (EMT) process. This would lead to a feed-forward loop. Interestingly, the idea that the centrosome can also act as a key coordinator of cellular processes unrelated to microtubule organization, acting for example as a stress sensor, has emerged in recent years. Hence, in addition to well-known cellular stresses such as those induced by DNA damage, oxidative stress, centrosomes abnormalities can also regulate cell cycle arrest and cell senescence through the release of inflammatory mediators. Eukaryotic cell division is a central process that requires complex changes in cytoskeletal organization and function. In recent years, the relevance of Rho GTPases and p38 MAPK in the regulation of many aspects of cell cycle transition, mitosis, and cytokinesis is emerging. Many of these factors and processes have been associated with CIN and inflammation by activating the cGAS-STING pathway. However, the precise nature of these interactions to promote metastasis needs to be fully characterized. Emerging evidence associates CIN to both, promotion and suppression of anti-tumor immunity depending on the type and origin of the tumor. In addition to the well-characterized role of p38 in inflammation and immunity, cell cycle arrest is also regulated by p38, which directly or indirectly influences motor proteins, microtubule dynamics, and centrosome activity. Notably, increasing numbers of evidence points to p53 as a common protein among the different involved pathways. Therefore, in the next future, it will be of great interest to establish the functional significance of centrosomal p53 and p38 activity in relation to various structural centrosome proteins and kinases that regulate them under physiological and pathological conditions.

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