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Nuclear assembly as a target for anti-cancer therapies

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Current anti-cancer therapies have a great deal of undesirable side effects; therefore, there is a need to develop efficient and cancer cell-specific new drugs without strong dose-limiting side effects. In my opinion, mechanisms of nuclear assembly and organization represent a novel platform for drug targets, which might fulfill these criteria. The nuclear stiffness and organization of some cancer types are often compromised, making them more vulnerable for further targeting the mechanisms of nuclear integrity than their normal counterparts. Here I will discuss the nuclear organization of normal cells and cancer cells, the molecular mechanisms that govern nuclear assembly with emphasis on those that, in my view, might be considered as targets for future anti-cancer therapies.

Pitfalls of Current Anti-Mitotic Drugs

Currently the most efficient anti-cancer chemotherapy agents are the cytotoxic drugs that target cancer cells, in a most vulnerable state, during mitosis.[1,2] These include the microtubule-binding taxanes (e.g., paclitaxel) that stabilize and vinca alkaloids (e.g., vinblastine) that destabilize microtubule polymers.[3] Both promote abnormal spindle assembly, chromosome misalignment, consequent activation of the spindle assembly checkpoint (SAC), and induce prolonged mitotic arrest and mitotic cell death.[4] However, cancer cells often adapt to these drugs and exit mitosis in a process called mitotic slippage.[5] Moreover, these drugs target not only mitotic cells but also affect the microtubule cytoskeleton functions of non-proliferating cells. They disrupt the interphase microtubule bundles of quiescent neuronal cells, along which molecular and vesicular transport occurs. Neurotoxicity is therefore one of the most common dose-limiting side effects of microtubule-targeting drugs.[6] Hence, there is a need to develop new anti-mitotic drugs, which by targeting specific mitotic proteins and mechanisms would achieve a similar level of anti-cancer efficacy without the unwanted side effects on non-proliferating cells. Such new targets included mitotic kinases (e.g., PLK1 and Aurora kinases) and mitotic motor proteins (e.g., Eg5 and CENPE) required for spindle assembly, chromosome alignment, and segregation. Their inhibition also induces SAC-mediated mitotic arrest and leads to mitotic cell death.[1] Although these new anti-mitotic drugs are highly specific in vitro and had some efficacy in xenograft models, they were so far less convincing in clinical trials than the microtubule-targeting drugs.[7,8] The reasons for these disappointing clinical results might be the low mitotic index (i.e., low number of cells undergoing division) of certain human tumors[1,7] and strong neutropenia, the main dose-limiting toxicity of the new anti-mitotic drugs.[7,9] Neutropenia refers to an abnormally low number of neutrophil granulocytes, the most abundant type of white blood cells. The reason why this occurs as a side effect is that during their development neutrophils frequently divide. Anti-mitotic drugs are not cancer cell-specific; they target every dividing cell, including neutrophils, and thus neutropenia is a consequence of their activity. Future anti-cancer drugs should therefore possess a larger therapeutic window and exert a higher-level cancer cell-specificity. One strategy to achieve this goal might be to develop new drugs that are synthetic lethal with mechanisms of cancer cell-specific hallmarks. In my opinion such new drug targets are the molecular mechanisms of nuclear assembly and organization because some of these mechanisms might get compromised during tumorigenesis, making the nuclei of these cancer cells more vulnerable than their normal counterparts. Below I will discuss the nuclear organization of normal cells and cancer cells, the molecular mechanisms that govern nuclear assembly, and I will hypothesize about the usefulness of targeting some of these mechanisms in future anti-cancer therapies.

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Nuclear Organization of Normal Cells

The nucleus contains the genome of the eukaryotic cell, whose precise organization is essential for normal cell function. The structure that defines the nucleus is the nuclear envelope (NE), a sub-domain of the endoplasmic reticulum (ER) (**Fig. 1**).[10,11] The NE is composed of outer nuclear membranes (ONM) and inner nuclear membranes (INM) with different protein compositions, which are fused at the sites of nuclear pore complex (NPC) insertion. Underlying the INM is the nuclear lamina, which is mainly composed of intermediate lamin filaments. In vertebrates, lamin proteins are grouped into A-type lamins (lamin A, Δ10, and C) encoded by the *LMNA* gene and B-type lamins (lamin B1

and B2)

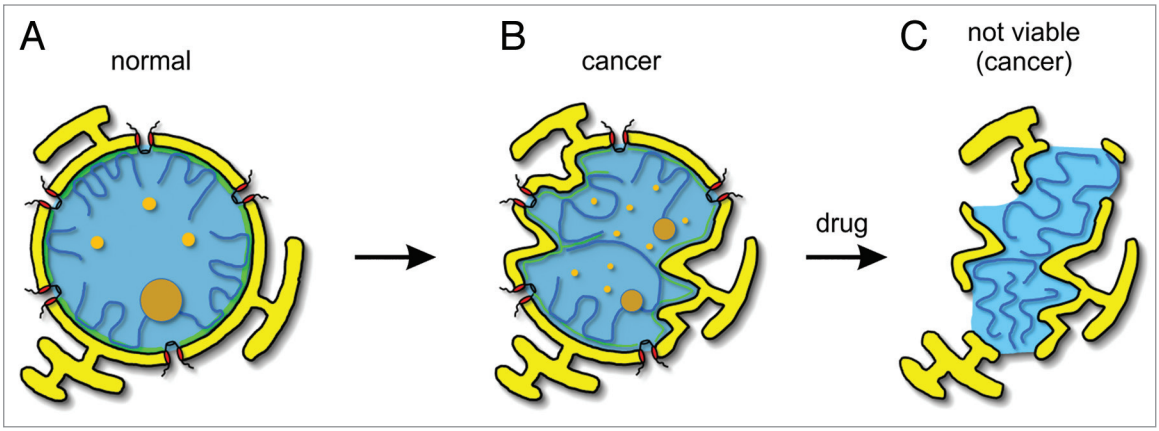

Figure 1. Nuclear organization. (**A**) The nuclear shape of most normal cells is oval. Nuclear envelope (yellow) is penetrated by the nuclear pore complexes (red). Underneath the nuclear envelope is the nuclear lamina (green), which provides the stiffness to the NE and serves as a tethering surface for chromosomes (blue lines). (**B**) Several cancer types are characterized by abnormal expression of lamins (particularly A-type), altered chromatin organization, and multi-lobulated nuclear shape. Other changes involve enlargement or fragmentation of the nucleolus (brown, large circles) and promyelocytic leukemia (PML) bodies (orange, small circles). Note that all these changes might not occur simultaneously in every cancer type. (**C**) Possible nuclear appearance of cancer cell nuclei after the treatment with drugs that interfere with mechanisms of nuclear assembly and organization.

encoded by *LMNB1* and *LMNB2* genes.[12,13] While B-type lamins are expressed in every somatic cell, A-type lamins are absent from highly pluripotent and rapidly dividing cells and are present only in differentiated cells. Lamins are alternatively spliced, and the ratio between the expressions of individual lamin isoforms is characteristic of each cell type.[14,15,16] Lamins mainly form homodimers, which assemble into head-to-tail homopolymers. These polymers then laterally assemble into filaments, which form a lattice of remarkably regular arrangement underneath the INM.[17,18] During maturation most lamins are C-terminally farnesylated. While this short lipid chain is retained on B-type lamins and anchors the proteins in the membranes, the farnesylated C-terminal part of lamin A is enzymatically cleaved after its incorporation into lamin polymers. The stabilization and organization of lamin filaments underneath the INM also requires lamin-associated membrane proteins, such as lamin B receptor (LBR), diverse LAP2/emerin/MAN1 (LEM) domain-containing proteins, and others.[12,13]

Nuclear lamina confers the shape, elasticity and the stiffness to the NE. The stoichiometry of A-type and B-type lamins correlates well with the mechanical stress the cells experience within a tissue.[16] In soft tissues such as liver or brain, A-type lamins are relatively low expressed, while in stiff tissues such as heart or muscle A-type lamins increase (up to 30-fold) to withstand the mechanical stress and to limit the potential disruption of the chromatin. B-type lamins are constitutively expressed and correlate much less with nuclear stiffness.[16,19]

By tethering the chromatin to the NE, nuclear lamina also contributes to the non-random chromatin organization within the nucleus (**Fig. 1**). Developmentally coregulated genes often form clusters on chromosomes, which are associated and corepressed at the nuclear periphery in cells where they are not expressed. Human chromosomes associate with the nuclear lamina via roughly 1000 sharply defined domains. These interactions are known to change progressively during differentiation.[20] Genes and chromosomal domains that become internalized during certain differentiation steps are either immediately activated or are unlocked and prepared for activation during further differentiation steps. This suggests that the nuclear lamina often provides a repressive environment for chromosomal domains at the nuclear periphery whose three-dimensional organization is specific for certain cell types and differentiation states. Mutation or downregulation of lamins or lamin-associated proteins results in disorganized lamin filaments[21] and deformed, multi-lobulated, and fragile nuclei,[22,23] which are often observed in human diseases such as cancer.[24-26]

Nuclear Organization is Disrupted in Cancer Cells

Cancer is initiated by genetic processes such as genome instability, genome rearrangements, or specific gene mutations, amplifications, or deletions, followed by epigenetic modifications, which ultimately lead to altered gene expression and result in deregulated cell proliferation. In cancer cells, nuclear size and shape are frequently altered.[24,25] Cancer-related morphological changes include NE invaginations, multi-lobulation, malleable and passively distorted nuclei, and altered appearance of heterochromatin, nucleoli, and nuclear bodies[27-29] (**Fig. 1**). Although all these features do not occur simultaneously, they are often used individually in the clinical diagnosis of cancer, in the assessment of the degree of the malignancy, and for prognostic and predictive indications of the disease state.[27-30]

Lamins, the most important architectural elements of the nucleus, are often aberrantly expressed or localized in cancer cells, and it is likely that this contributes to the multi-lobulated nuclear shape often observed in different cancer types[31] (**Fig. 1**). Many poorly differentiated cancer types exhibit downregulation of A-type lamins and concomitant irregularities in their nuclear shape. For example, in small cell lung cancer (SCLC) cells A-type lamins are either not or only weakly expressed, while in non-SCLC cells they are normally expressed but frequently mislocalized in

the cytoplasm.[32-34] In colon cancers,[35] gastric cancers,[36,37] breast cancers,[38,39] and diffuse large B-cell lymphomas,[40] the expression of A-type lamins is also strongly reduced, and this feature correlates with increased disease recurrence and poor patient prognosis. Consequently, the nuclei of these cancer types are often fragile and lobulated, and in breast cancer cells, they were shown to contain massive NE membrane invaginations[27,28] (**Fig. 1**). The nuclei of prostate cancer cells[41] and of some other cancer types[42] are not only lobulated but also contain structures called nuclear blebs, protrusions from the nuclear surface enriched in lamin A/C but deficient in lamin B. Further examples with multi-lobulated nuclear shape are ovarian cancers,[43] papillary thyroid cancers,[27] leukemias,[44] and different B-cell lymphomas.[40,45,46] In conclusion, altered lamin expression or localization and disrupted stoichiometry between A- and B-type lamins can change the elastic properties of the NE,[16] which renders it unable to withstand cytoskeleton-[47,48] and chromosome-based[49,50] forces and leads to misshapen nuclei. Consistently, downregulation of lamin A/C in non-cancer primary breast epithelial cells results in nuclear alterations similar to those observed in breast cancer cell.[38] Moreover, mutations in *LMNA* and other genes encoding for proteins of nuclear lamina results in heritable diseases called laminopathies,[51] which are also characterized by fragile[52] and multi-lobulated nuclear shape.[53] Therefore the nuclear lamina alterations might directly account for the cancer-related changes in the nuclear morphology. However, it is important to note that several other cancer types display normal nuclear shape and that there is no simple universal pattern of lamin expressions for all cancer types.[31,45,46,54]

It is unclear whether the abnormal nuclear organization observed in cancer cells is the cause or the consequence of transformation and tumor progression. Lamins might modulate gene expression not only indirectly through influencing global chromatin organization but also by directly interacting with transcription factors that affect cellular proliferation, differentiation, and apoptosis.[55,56,57] Therefore, the absence of lamins from tumors derived from tissues where they are normally present led to the hypothesis that lamins might be directly involved in tumorigenesis. However, this tempting hypothesis is contradicted by several lines of evidence. *LMNA* gene contains the largest diversity of mutations that lead to rare human diseases. There are more than 20 distinct laminopathies associated with approximately 400 different mutations in the human *LMNA* gene.[13,51] Most of these mutations affect the assembly, dynamics, or function of lamin filaments and result in deformed, multi-lobulated, and fragile nuclei and abnormal heterochromatin structure, similar to the nuclear abnormalities observed in cancer cells.[21,58,59,60] However, none of the mutations in lamin or in lamin-organizing proteins are known to be tumorigenic, and patients with laminopathies are not more susceptible to cancer development than healthy individuals with normal nuclear architecture. Moreover, loss of lamin A from human fibroblast cells[61] or ovary surface epithelial cells[43] results in reduced mitosis and retarded cell growth, which at least in part might be explained by the active role of lamin A in nuclear localization of the cell cycle regulator retinoblastoma protein (Rb).[61] Finally, although higher order chromatin organization is commonly altered in cancer cells, this does not necessarily lead to tumorigenic transcriptional changes. In breast cancer for example, several genes have been identified that specifically change their nuclear position only in cancer cells. However, the absence of transcriptional changes associated with the movement of these genes suggests that these changes are not responsible for tumorigenesis.[62] In conclusion, although precise nuclear organization is essential for normal cellular function, up to now altered nuclear architecture has not been shown to drive cancer development, and therefore, it is more likely to be a consequence of cell transformation and tumor progression. Accordingly, nuclear irregularities arise dynamically during interphase following oncogene induction.[48,63] Since the nuclear architecture of many cancer cells is abnormal, this hallmark might improve cancer cell-selectivity in therapies using mechanisms of mitotic nuclear assembly and nuclear organization as targets (**Fig. 1**).

Mitotic Nuclear Dynamics

The nuclear structure is disassembled and reassembled during every cell division to allow cytoplasmic spindle microtubules to segregate the duplicated sister chromatids. These dynamics are under precise spatial and temporal control of mitotic kinases and phosphatases.[64,65,66]

Mitotic nuclear disassembly is controlled by cyclin-dependent kinase 1 (CDK1)[67,68,69] and other mitotic kinases that function downstream of its activation, such as protein kinase C (PKC),[70,71] Aurora A,[72] polo-like kinase 1 (PLK1),[73] NIMA-related kinases,[68] and vaccinia-related kinase 1 (VRK1).[74,75,76] They phosphorylate proteins of nuclear lamina and NPC to disrupt their interphase molecular interactions. In support of their critical role, inactivation or inhibition of these mitotic kinases either blocks or delays various steps of nuclear disassembly. For example, VRK1 kinase is activated during mitotic entry upon degradation of its interphase inhibitor macroH2A1.[77] It relocalizes to the nuclear periphery[75] and phosphorylate barrier-to-autointegration factor (BAF or BANF1) to release it from DNA and LEM domain-containing INM proteins[75,76] (**Fig. 2**). Inhibition of VRK1 thus prevents a late but essential step of nuclear disassembly. As a consequence of massive protein phosphorylation events, during NE breakdown soluble proteins become dispersed into the cytosol while membrane proteins become mobile and, together with the NE membranes, absorbed into the oscillating ER network.[78]

CDK1 promotes mitotic progression until the alignment of mitotic chromosomes on the metaphase plate and the correct bipolar attachment of all the kinteochores with spindle poles is achieved. This turns off the SAC and promotes anaphase onset.[65,66] Subsequently, members of the protein phosphatase 1 (PP1)[79] and 2A (PP2A)[74] family are activated. They counteract CDK1 and other mitotic kinases to allow the assembly of the interphase nucleus.[74,79] Chromatin decondensation is an important step of post-mitotic nuclear assembly. Although its exact mechanism is still unclear, likely players are PP1, which acts by dephosphorylating histone H3,[79] AAA-ATPase p97,

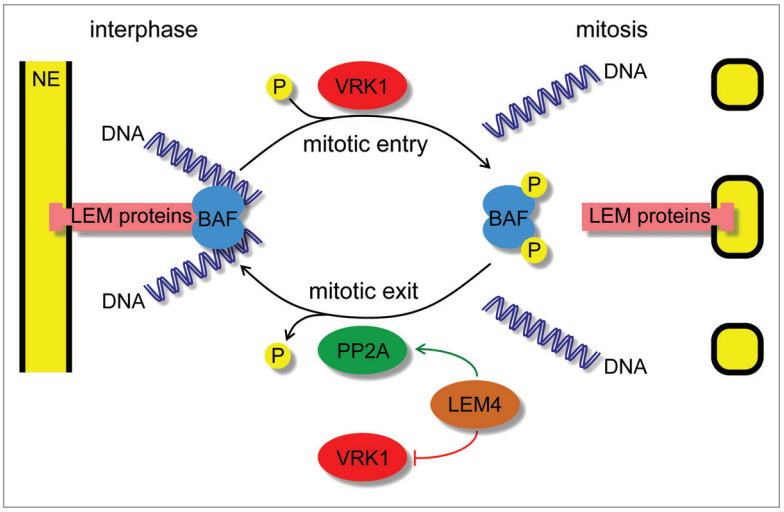

Figure 2. Mitotic regulation of BAF function. During interphase BAF binds as a dimer (light blue) to one LEM domain-containing integral nuclear envelope protein (pink) and to two DNA helices (dark blue). During mitotic entry VRK1 (red) phosphorylates BAF to disrupt its interactions and contributes to nuclear envelope breakdown. During mitotic exit LEM4 (brown) inhibits VRK1 (red) and promotes PP2A (green) to dephosphorylate BAF and to enable its function in post-mitotic nuclear reassembly.

which extracts the polyubiquitylated Aurora B histone kinase from chromosomes,[80] and the small Ras-like GTPase Ran, which acts in a still poorly understood manner.

The first step of NE reformation is the attachment of ER membranes[81,82,83] to the chromatin surface. Although direct lipid-chromatin interactions might play a role, this interaction is mainly mediated by trans-membrane and membrane-associated proteins. A large population of INM proteins possesses a highly basic nucleoplasmic domain that can directly bind to DNA.[84] The INM proteins function redundantly, thus their individual inactivation has only a minor effect on NE assembly and even simultaneous inactivation of several only delays but does not prevent the recruitment of membranes to the chromatin surface.[75,85,86] Other INM proteins interact with chromatin through specific adaptor proteins. These interactions are controlled spatially by the small GTPase Ran and temporally by protein dephosphorylation. GTP-loaded Ran is generated in the vicinity of chromosomes[87] and mediates the release of the inhibitory importin receptors from their target proteins, providing spatial control of NE reformation.[11] As a specific example, during mitotic exit RanGTP releases importin-β from the chromatin-binding domain of LBR,[88,89] thereby allowing its binding to histones H3/H4[90] and HP1.[91]

In the subsequent steps, chromatin-attached membranes start to spread from the "peripheral" margins of the separating chromatin to surround the entire chromatin mass and enclose it in a single nuclear compartment. There is constant membrane supply from the ER, and manipulation of ER structure was shown to influence NE assembly.[70,82,92,93] The recruited membranes on the chromatin surface are organized by BAF, which as a dimer can bind to one LEM domain of an INM protein and to two DNA helices (**Fig. 2**).[64,94,95] Consistently, inactivation of BAF results in deformed, multi-lobulated nuclei, with NE membranes trapped between individual chromosomes.[15,75,96] The localization and function of BAF is regulated by phosphorylation, which is temporally controlled by LEM4 (**Fig. 2**).[64] During mitotic exit LEM4 binds to VRK1, BAF's mitotic kinase, and inhibits its further activity on BAF.[74] Concomitantly, LEM4 also binds to and activates a complex of PP2A (i.e., PP2A-B55α) to dephosphorylate BAF and to allow its re-association with chromatin and INM protein.[74] This particular PP2A complex has been further implicated in other mitotic functions and is the only protein phosphatase essential for mitotic exit.[97] Recently PP4C, which is known to form complexes with different PP2A subunits,[98,99] was also suggested to influence the phosphorylation state of BAF.[100] Nevertheless, during mitotic exit BAF rapidly and strongly accumulates on the central surface of the chromatin "core" regions, which surround the anaphase chromatin mass, on one side facing the spindle microtubules and on the other facing the midzone microtubules.[75,101] The "core" region is a thick, electrondense structure mainly devoid of membranes. One of the features of the "core" region is that it rapidly shrinks with mitotic progression prior to the spread of the NE membranes from the peripheral regions toward the central region.[75,101] The exact function of BAF during NE membrane organization is still unclear; however, it may synchronize different membrane and chromatin events during NE assembly to enable the incorporation of the entire chromatin mass into a single nuclear compartment.[75]

Concomitantly with NE reformation, NPCs are also assembled post-mitotically via mechanisms that are different from those used during interphase NPC assembly.[102] NPC subcomplexes form pre-pores on the chromatin surface, which are then incorporated in the NE during membrane spreading on the chromatin surface. In the final step of NE assembly, remaining holes in the NE membranes may be fused by SNARE proteins.[103] However, since these holes can also be occupied by NPCs, the membrane fusion machinery is less important during NE assembly than was initially anticipated. Upon the formation of a closed NE, nucleocytoplasmic transport is reactivated. The lamin proteins are actively imported into the nuclei[104] where they are polymerized and organized underneath the INM to provide shape, elasticity, and stiffness to the nuclei.

Synthetic Lethality with Abnormal Nuclear Architecture of Cancer Cells

In genetic studies using different experimental model organisms, synthetic lethality is based on the fact that inactivation of one gene makes the cell vulnerable for the inactivation of the other gene, while neither of these two genes is essential on its own. In anti-cancer therapies similar synthetic lethality might be achieved between cancer cells and drugs, in case the cancer cell-specific molecular lesions sensitize the cancer cells for drugs inhibiting particular protein functions. The value of

such an approach is that normal cells without such lesions will be unaffected. As discussed earlier, the nuclear architecture of different cancer cells is compromised and unable to withstand cytoskeleton-[47,48] and chromosome-based[49,50] forces and often so malleable that they can be crushed during biopsies (e.g., SCLC cells). This suggests that future drugs hitting mechanisms of nuclear assembly and organization to further weakening the NE structure might result in a synergistic effect and specific killing of such cancer cells (**Fig. 1**). In support of this hypothesis, several synthetic lethality interactions have been described in the literature between different NE proteins.[86,105] For example, B-type lamins were shown to be dispensable in mouse cells expressing A-type lamins but essential in those where lamin A was suppressed.[47,106,107]

Drug targets that are potentially synthetic lethal with abnormal nuclear organization of some cancer types might be identified either via phenotypic and synthetic lethality screens or by literature mining. Based on the latter one, in my opinion, BAF represents one of the most promising targets for specifically killing cancer cells with altered nuclear appearance. I base this assumption on facts that BAF is often highly expressed in some cancer types (e.g., ovarian cancer, endometrial cancer, breast cancer, colorectal cancer, lung cancer, prostate cancer, glioma, melanoma, and lymphoma),[108,109] and it is an important player of post-mitotic nuclear assembly[75,85,96] whose downregulation[75,85] or mutation in humans[96] delays NE formation and induces strong nuclear irregularities. Due to its small size and relatively flat protein surface[94,95] without suitable binding pockets for small molecular weight inhibitory compounds, BAF is considered to be undraggable. To overcome this, new anti-mitotics might be designed against its mitotic regulators (**Fig. 2**). First of all, the dephosphorylation of BAF might be targeted because this is essential for its correct localization and function during mitotic exit.[64] Therefore, drugs interfering with either the inhibitory interaction between LEM4 and VRK1, the mitotic kinase of BAF, or with the activating interaction between LEM4 and PP2A, the mitotic phosphatase of BAF, might be developed (**Fig. 2**).[74,75] Consequently, they would enhance the phosphorylation of BAF, hereby weakening its interactions with LEM domain containing INM proteins and DNA.[94,95] A second strategy might rely on interfering with the nuclear structure during mitotic entry by inhibiting BAF's kinases VRK1 and VRK2. Consistently, depletion of VRK1 from breast cancer cells results in retarded tumor growth and reduced incidence of metastasis in a murine orthotopic xenograft model.[110] Furthermore, the first inhibitor of BAF phosphorylation with an in vitro anti-cancer activity was recently isolated from a species of tree used in traditional medicine.[111] Another approach might aim to target the inhibitory interaction between LBR and importin-β because perturbation of this interaction also results in NE assembly failure, abnormal chromatin decondensation, and daughter cell death.[88] Finally, B-type lamins are also promising targets because they are highly expressed in several cancer types,[31,108,109] and they might become essential for survival of cancer cells with reduced expression of A-type lamins. Since lamins are also considered to be low-druggable, they might be targeted indirectly by inhibiting their regulators. Such examples include AKAP149, which via promoting PP1 mediates the assembly of B-type lamins into nuclear lamina,[112,113] and farnesyltransferase enzymes that add a 15-carbon farnesyl group to the C-terminal of most of the lamins to keep the B-type lamins anchored to the membranes.[12]

Currently, only a few drugs exist that directly target mechanisms of nuclear assembly and organization, but interestingly, they can induce cancer cell death. For example, the farnesyltransferase inhibitor R115777 inhibits the growth of B-cell lymphoma[114] and breast and ovarian cancer cells[115] in vitro and reduces the tumor growth in xenograft model systems. Since lamins are not the only substrates of farnesyltransferases, it is possible that the main anti-tumor activity of this inhibitor is achieved via other substrates, such as the small GTPase Ras proteins. Betulinic acid inhibits the expression of lamin B1 in pancreatic cancer cells and induces dose-dependent anti-cancer activities in both in vitro cultures and xenograft model systems.[45] Covalent (NMS-859) and allosteric (NMS-873) inhibitors of p97, an AAA-ATPase known to extract the polyubiquitylated Aurora B from chromatin during post-mitotic nuclear reassembly,[80] have antiproliferative effect in vitro on few cancer types.[116] However, it is possible that the anti-cancer activity is linked to other roles of p97, such as the ER-associated protein degradation. Obtusilactone B is a new inhibitor of BAF phosphorylation by VRK1, and it also inhibits the proliferation of few cancer cells in vitro.[111] In line with this, drugs that directly or indirectly activate PP2A (e.g., ceramide, FTY7220, dithiolethione, etc.), the mitotic phosphatase of BAF, also have anti-cancer activities in different malignancies like prostate cancers, breast cancers, lung cancers, or leukemia.[117,118] Finally, microtubules have an influence on the nuclear shape,[48,63] and they are directly involved in NE breakdown[119,120] and reformation.[101] Therefore, microtubule-binding drugs, at least in part, could interfere with the abnormal nuclear structure of some cancer types.

One possible side effect of targeting the mechanisms of nuclear assembly and organization in future anti-cancer therapies might be the artificial induction of laminopathy-like symptoms, such as muscular dystrophies or lipodystrophies. This is suggested by the fact that laminopathies are caused by mutations in different lamina proteins such as lamin A, BAF, LBR, or emerin.[51,96] However, laminopathies are developmental disorders, and therefore, it is possible that they might require more time to appear than the duration of the anti-cancer therapy itself. Second, similarly to other anti-mitotic therapies, reduced levels of platelets and blood cells, such as thrombocytopenia or neutropenia, might be also induced. Interestingly, however, neutrophils have multi-lobulated and malleable nuclear structures, probably required for the extrusion of their chromatin fibers to trap and kill bacteria at the sites of infection.[121] It is likely that reduced expression of BAF[108,109] and its binding partners emerin, LAP2β, lamin A/C, and lamin B2[122,123] might account for such nuclear appearance. Therefore, targeting proteins that are highly expressed in cancer cells but repressed in neutrophils could lead to at least the terminally differentiated neutrophils being resistant to these new drugs.

Concluding Remarks

Cancer is one of the leading causes of mortality worldwide. Anti-cancer drugs, in addition to surgery, have been proven to be beneficial for patients with particular cancer types; however, their effectiveness is often limited by dose-limiting toxicities. Therefore, there is a need to develop new drugs that can achieve efficient and cancer cell-specific effects without undesirable side effects. In my opinion, particular molecular mechanisms of post-mitotic nuclear assembly and nuclear organization represent attractive new targets for such next-generation anti-cancer therapies. This strategy relies on putative synthetic lethality between the altered nuclear structure of some cancer types and drugs targeting, directly or indirectly, BAF, B-type lamins, VRK1, VRK2, and other similar proteins that are important for proper assembly and organization of the nuclei and are clearly expressed or overexpressed in these cancer types.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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