A potential role for genome structure in the translation of mechanical force during immune cell development

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ABSTRACT
Immune cells react to a wide range of environments, both chemical and physical. While the former has been extensively studied, there is growing evidence that physical and in particular mechanical forces also affect immune cell behavior and development. In order to elicit a response that affects immune cell behavior or development, environmental signals must often reach the nucleus. Chemical and mechanical signals can initiate signal transduction pathways, but mechanical forces may also have a more direct route to the nucleus, altering nuclear shape via mechanotransduction. The three-dimensional organization of DNA allows for the possibility that altering nuclear shape directly remodels chromatin, redistributing critical regulatory elements and proteins, and resulting in wide-scale gene expression changes. As such, integrating mechanotransduction and genome architecture into the immunology toolkit will improve our understanding of immune development and disease.

KEYWORDS
chromatin; genome biology; Hi-C; immune; mechanosensory; mechanotransduction; nucleus; nuclear lamin; nucleoskeleton; tensegrity

Introduction

Immune cells are exposed to a vast array of different microenvironments as they travel through the body in search of foreign agents. The mammalian immune system is remarkably effective at clearing pathogens and tumors while leaving commensal bacteria and healthy tissue intact.1 Tight self-regulation and rapid responses maintain the balance of pro-inflammatory and anti-inflammatory factors at a healthy level, while allowing high levels of inflammation at local sites of infection.2 However this balance is disturbed in autoimmune disorders, where local inflammation is maintained at damaging levels without the presence of a pathogen, destroying otherwise healthy tissue.3 Further, global low grade inflammation gives rise to the co-morbidities associated with obesity.4 Much is already known about the environmental and genetic factors that contribute to the development and differentiation of the wide range of pro- and anti-inflammatory cells, particularly in regard to cytokines and protein-altering mutations.5,6 However, it remains possible that the mechanical processes (i.e. mechanotransduction7) associated with the physical environment also directly contribute to development of immune cells in vivo.

Chemical signals regulate cell differentiation

Immune cells are surrounded by a chemical milieu in vivo,8 which induces and directs immune cell differentiation.5 Many cell types, including immune cells, secrete cytokines into the extracellular matrix (ECM). When cytokines come into close proximity with a cell with an appropriate receptor, the cytokine will bind, initiating a signal transduction cascade that activates or represses target genes9 – often transcription factors.10 This in turn induces further changes in gene expression, often upregulating the original cytokine(s)9 and creating a positive feedback loop. For example, exposing a naïve CD4 + T helper (Th) cell to the interferon (IFN)-γ cytokine upregulates the T-bet transcription factor, which in turn upregulates IFNγ.11 This feedback loop maintains the newly differentiated pro-inflammatory Th1 cell.5

In an appropriate cytokine environment, CD4+ T helper cells can differentiate into a wide range of
subtypes in addition to Th1 cells.\textsuperscript{5,12,13} The mechanisms of induction and behavior of some of these subtypes (\textit{e.g.} allergen associated Th2 cells,\textsuperscript{14} pro-inflammatory Th17 cells,\textsuperscript{15} and anti-inflammatory Treg cells\textsuperscript{16}) are well characterized. In contrast, the induction and behavior of other T helper cell subtypes, including Tfh, Tr1, Th3, and Th9, is less well understood.\textsuperscript{9} However, even the classical subtypes are more plastic and variable than originally thought, particularly in humans.\textsuperscript{17}

**Spatial DNA organization modulates immune cell development**

We have gained significant insight into the effects of cytokines on differentiation and disease,\textsuperscript{5,6} and recent progress has also been made into the role of genetic variation in the human immune response.\textsuperscript{18} One area of interest is the role of regulatory variants in immune cells, where recent studies of expression quantitative trait loci (eQTL) have shown that genetic variants located in regulatory regions cause immune cells to be more or less receptive to certain environmental signals.\textsuperscript{19,20} Both studies identified many more cis-eQTLs (<1 MB from the promoter) than trans-eQTLs (>1 MB from the promoter, or on a different chromosome), most likely because multiple testing dramatically reduces the power to detect long-range eQTLs.\textsuperscript{21}

The trans-eQTLs that were identified in Fairfax et al.\textsuperscript{19} and Lee et al.\textsuperscript{20} were attributed to cis-eQTLs affecting major pathway regulators.\textsuperscript{19,20} However, trans-eQTL effects can also be directly mediated by the spatial organization of DNA, which is critical in immune cell development. This is best illustrated by the T helper 2 locus control region (Th2 LCR), which has long been known to regulate expression of Th2 cytokines (Interleukin(II)-4/5/13) in \textit{cis}.\textsuperscript{22} Recent experiments have demonstrated that the Th2 locus also regulates key Th1 (IFN\textgamma) and Th17 (Il-17) cytokines in mice – even though they are found on different chromosomes.\textsuperscript{23} This critical stage in the regulation of T cell differentiation\textsuperscript{23} is achieved by the formation of a spatial connection between 3 different chromosomes, possibly mediated by a transcription factory.\textsuperscript{24} Disruption of this interchromosomal connection, by deleting the DNase I hypersensitive region RHS6 of the Th2 LCR, increases the proportion of Th17 cells produced.\textsuperscript{23,25} Thus, this raises the possibility that genetic variants within this LCR could result in dysregulated Th cell differentiation and an autoimmune disorder.\textsuperscript{26}

Disruption of the Th2 LCR has a major impact on Th cell development, therefore it is reasonable to assume that variants with this effect are unlikely to become common in the population.\textsuperscript{27} However, mutations that modulate, instead of disrupt, the activity of regulatory regions are common polymorphisms.\textsuperscript{18} As with many complex disorders,\textsuperscript{28} immune cell enhancers are enriched for autoimmune-associated single nucleotide polymorphisms (SNPs).\textsuperscript{18} Moreover, these enhancers frequently form spatial connections with promoters more than 500kb away, even if there are promoters that are more proximal.\textsuperscript{29}

While the linear order of elements within a chromosome is important, DNA has a 3-dimensional spatial organization that is a store of epigenetic information during cellular and organismal development. DNA is flexible and forms many chromatin loops, which are clustered into topological domains.\textsuperscript{30,31} These topological domains interact with other domains of a similar chromatin state, creating a hierarchical organization of DNA.\textsuperscript{32} This means that regulatory elements can interact with gene promoters from many kilobases away, or even on different chromosomes.\textsuperscript{25,33,34} Some of these interactions are mediated by transcription factories: regions of the nucleus containing a high density of active RNA polymerase and other transcriptional components, resulting in high levels of transcription of proximal loci.\textsuperscript{35-39} If a mutation in one locus affects the composition or localization of the transcription factory,\textsuperscript{40} it could disrupt the expression of some or all of the genes associated with that factory.\textsuperscript{40}

The accurate annotation of trait-associated variants requires the integration of spatial information because of the interleaved organization of the genome. This requirement is illustrated by the SNP, rs9930506 which is strongly associated with obesity.\textsuperscript{41} rs9930506 is located in an intron of the \textit{FTO} gene. \textit{FTO} codes for the fat mass and obesity-associated protein and was initially thought to be the target of rs9930506 activity.\textsuperscript{42} However, chromatin capture techniques, such as 4C which identifies spatial interactions between genomic loci, and subsequent eQTL analysis revealed that rs9930506 was localized to an enhancer that regulates 2 different genes, \textit{IRX3} and \textit{IRX5}, 600kb and 1.2Mb away respectively.\textsuperscript{43,44} These genes code for the Iroquois homeobox proteins 3 and 5, which are
transcriptional regulators involved in the differentiation of adipocyte progenitor cells into either lipid-storing white adipocytes or lipid-utilizing beige adipocytes, the latter being protective against obesity. Thus, by only considering the linear organization of DNA, analyses into the function of rs9930506 incorrectly focused on FTO for many years, before IRX3 and IRX5 were investigated in relation to this obesity associated SNP.

As with the FTO SNP rs9930506, integrating spatial genomics data into genome wide association study (GWAS) analyses is likely to produce novel and actionable insights into the genetic basis of complex autoimmune disorders (e.g.,). Moreover, since the effects of some variants are only apparent under certain environmental conditions or at a specific point in development, a range of relevant stimuli, both chemical and mechanical, should be used to investigate the functionality of a SNP.

**Do mechanical forces regulate immune differentiation and disease?**

The tensegrity model proposes that cell shape is maintained by pre-stressed networks containing both stiff and flexible structures held under constant tension: the cyto- and nucleo-skeletons. The cyto- and nucleo-skeletons are mechanically linked via a protein complex that spans the nuclear envelope, known as the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex. This pre-stressed network provides a conduit through which mechanical forces can have immediate effects on nuclear shape, altering chromatin organization and dynamics.

Immune cells are exposed to a wide range of mechanical environments. The physical characteristics of these environments range from shear stress in the blood stream, to cellular deformation during diaplasia, and the complex mechanical environments of the bone marrow, organs, tissues, and tumors. Each of these environments plays a role in the development or behavior of immune cells, and ultimately the overall immune activity in the human body. However, mechanosensing in mature immune cells has remained relatively understudied due to the commonly held belief that mature immune cells lack myosin IIB and Lamin A, which are crucial mechanosensory components of the cyto- and nucleo-skeleton, respectively. Despite this we know that Lamin A plays a critical role in T cell activation and that immune cells respond to mechanical forces throughout their lifetime.

Haematopoietic stem cells (HSCs) develop in the bone marrow, a complex tissue that is very soft in the center, but increases in stiffness toward the periphery. Early HSCs divide symmetrically in the soft interior, but once reaching the stiff ECM in the periphery of the marrow, they divide asymmetrically (Fig. 2A). This occurs because a soft matrix represses polarization of myosin IIB, a mechanosensory component of the actin cytoskeleton. As the HSC reaches the stiff matrix, myosin IIB becomes polarized and asymmetrically segregates during cell division, resulting in 2 daughter cells: a stem cell, and a differentiated cell containing the low myosin IIB levels characteristic of differentiating blood cells. Mature immune cells also respond to matrix stiffness; neutrophil-like HL60 cells alter cell and nuclear morphology, as well as chemotaxis speed and directionality, in proportion to substrate elasticity.

The mechanical environment directly influences cell fate determination in mesenchymal stem cells.

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**Figure 1.** Tensegrity architecture coordinates responses to mechanical signals. Cell surface receptors are mechanically linked to the nucleus via the cytoskeleton and LINC complex. These inter-connected skeletons can transduce mechanical signals, including fluid shear stress to rapidly remodel the cyto- and nucleo-skeletons.
by altering the composition of the nuclear lamina, which is composed of 2 intermediate filament subtypes; Lamin A/C and Lamin B form a mesh layer on the inner surface of the nuclear envelope. Lamin A/C has low elasticity, while Lamin B is more extensible; thus the ratio of Lamin A:B determines nuclear stiffness and is highly variable between cell types, correlating with the size of the forces they are exposed to. Stiff matrices (~100kPa) or shear stress induces high Lamin A and expression of osteoblast genes, whereas soft matrices (~1kPa) induce low Lamin A and expression of adipocyte or neuronal genes. Manipulation of Lamin A levels can reproduce these cell fate decisions, indicating that the increased Lamin A expression caused by mechanical forces influences gene expression in developing MSCs.

The flow of causality in this case demonstrates that the mechanical environment shapes the nucleoskeletal composition, which then allows all other gene expression changes to complete differentiation of the cell. This ensures that cells have the appropriate nucleoskeletal architecture for their environment.

The endothelial cells that line blood vessels are also highly responsive to shear stress; their nuclei flatten and align in the direction of blood flow. Endothelial cells within blood vessels also respond to the composition of the underlying basement membrane, which often stiffens as we age. Stiffening of the basement membrane directs changes in endothelial cells that affect their responses to fluid shear stress. Growth on a stiff matrix also alters the differentiation trajectory of MSCs in response to the cytokine transforming growth factor (TGF)-β. Thus, the mechanical environment alters cellular responses to

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**Figure 2.** Immune cells are exposed to a variety of mechanical environments. (A) During development in the bone marrow, Haematopoietic stem cells (HSCs) divide symmetrically (i) in the soft marrow, but divide asymmetrically upon reaching the stiff matrix (ii); one daughter cell maintains stemness, while the other begins differentiation. The differentiating cell migrates into the blood vessel by squeezing through the endothelial cell layer, which deforms the nucleus (iii). The cell is then subject to fluid shear stress in the blood stream (iv). This step is particularly important for the development of megakaryocytes into platelets. (B) During inflammation, the matured immune cell must then extravasate to enter the infected tissue. To migrate through the endothelial cell layer, the cell first makes contact with the endothelial cells (rolling adhesion, (i)), then becomes more strongly adherent (firm adhesion, (ii)), and finally undergoes diapedesis (iii). After successful migration, the cell may be exposed to a range of tissue microenvironments (iv,v). Finally, the cell may return to the blood stream (C), again deforming the nucleus to migrate through the endothelial cell layer, and once again becoming exposed to fluid shear stress.
mechanical and chemical signals affecting cell activity and differentiation.

The mechanical composition of the bone marrow niche may be sensitive to the compressive and tensile forces applied to bones, which could influence HSC differentiation. While there are currently no studies showing a direct link between bone loading, marrow composition, and HSC development, many groups have noted the connection between exercise or microgravity, and immune activity. For instance, chronic low-grade inflammation is a hallmark of obesity, and often leads to metabolic disorders such as type 2 diabetes. These disorders can be mitigated by exercise, i.e., increased bone loading, which reduces the peripheral white blood cell count of at-risk women. Conversely, astronauts regularly suffer from immune deficiency during spaceflight as a result of microgravity, i.e. severely reduced mechanical loading. The results of these studies seem contradictory, indicating that mechanical loading can both increase and reduce white blood cell count. However, it is possible that mechanical loading results in a regression to the mean, preventing the extreme phenotypes of both immune depletion and overstimulation. Although these effects could be due to cytokine or hormonal signaling, the mechanical forces applied to bone from gravity or exercise may affect immune cells directly, or via altered bone marrow composition.

**Immune cell shape changes during diapedesis**

Once blood cells have matured in the bone marrow, they enter circulation, where fluid shear stress from blood flow affects many immune cell types. Megakaryocytes are torn apart to produce immature thrombocytes, which continue to mature in the lamellar flow. Fluid shear stress prevents pseudopod formation and prevents immune cells adhering to endothelial cells, although this response can be modulated by inflammatory signals. Shear stress from blood flow is crucial for the activation of neutrophils, and encourages CD3+ T cell migration across the endothelium, also known as trans endothelial migration (TEM) or diapedesis. To complete diapedesis, cells must change their shape to fit between the endothelial cells, presenting a further mechanical challenge to the cell and nucleus.

Diapedesis is necessary at many stages of immune cell development, from leaving the bone marrow, to entering and leaving lymph nodes and other organs. Briefly, the immune cell first attaches to the endothelial cell, initiating an adhesion cascade, before polarizing and migrating through an endothelial cell junction. This paracellular route is most commonly observed, but some cells actually undergo transcellular diapedesis and migrate through the center of the endothelial cell. Either way, the cell must deform itself to leave or enter the blood vessel, resulting in changes to the immune cell. For example, in a recent study, Zimmermann et al. showed that reverse transmigration (i.e., migrating from the tissue to a vessel) enhances the proinflammatory behavior of macrophages compared to those that remain in the tissue. This observation can be explained by: 1) the possibility that proinflammatory cells are more inclined to migrate; or 2) the cell deformation during reverse transmigration altering macrophage gene expression to activate proinflammatory pathways. Migration is known to induce expression of β1-integrin in neutrophils, supporting the explanation that migration alters expression of pro-inflammatory genes.

Recently, Raab et al. have shown that migration through physiologic (mouse ear explant) and non-physiologic (PDMS micro-channels, collagen matrix) spaces much smaller than the nucleus can result in the nuclear envelope of dendritic cells rupturing. Prior to rupture, the nucleus undergoes extensive deformation, and some nuclei fail to rupture at all. When the nucleus loses membrane integrity, extensive DNA damage can occur. However, it remains unknown how nuclear deformation without rupture influences the spatial organization of DNA, and whether deformation results in programmed gene expression changes or simply a DNA damage response.

Microscopic and other observations indicate that chromatin reorganisation must occur during migration. However, the nuclear shape change that takes place may be due to mechanotransduction or programmed remodelling. When a mechanical force is directly applied to a cell, it must respond quickly to prevent damage, making mechanotransduction a likely response mechanism. However, diapedesis is a controlled process. Programmed chromatin remodelling could be initiated at any stage of...
diapedesis, pre-empting the nuclear shape changes to avoid damage during migration. In either case, nuclear remodelling must occur for the immune cell to complete diapedesis, and may result in widespread gene expression changes.\textsuperscript{54}

The nucleus is known to be a highly mechanosensitive organelle.\textsuperscript{107} This is supported by observations that cytoskeletal regulated changes to nuclear shape result in altered dynamics for heterochromatic foci\textsuperscript{52,104} and telomeres.\textsuperscript{52} Mechanosensitivity is not limited to the movement of chromatin and nuclear structure. Transcription factors, including NF-kB,\textsuperscript{105} and the chromatin remodeller HDAC3,\textsuperscript{108} have been observed to move from the cytoplasm to the nucleus in cells under mechanical stress.\textsuperscript{105,108} Physiological levels of stress have also been shown to disrupt protein complexes, notably this has included the dissociation of coilin from the survival motor neuron protein (SMN) deep within the nucleus.\textsuperscript{109} Finally, a recent study has shown that chromatin stretching in response to a directional force increased chromatin accessibility and resulted in higher gene expression.\textsuperscript{110}

In isolation, these responses seem insufficient to account for the highly specific gene expression changes that occur in response to mechanical forces. However, the combination of chromatin movement, a dynamic proteome, and interactions between these elements, may be sufficient to culminate in global but precise transcriptional changes.

Many proteins are associated with the nucleoskeleton and chromatin.\textsuperscript{39,111} These proteins include, but are not limited to: sumo1,\textsuperscript{112,113} a post-translational modifier of many nuclear proteins\textsuperscript{114,115}; the retinoblastoma protein\textsuperscript{116-118} which is critical to cell cycle control and differentiation\textsuperscript{119}; and a range of transcription-associated proteins and complexes.\textsuperscript{120,121} Mechanical directed movement of chromatin,\textsuperscript{51,52} including that which occurs during migration, may: 1) result in disruption or repositioning of transcription factories,\textsuperscript{39} chromatin remodelling complexes,\textsuperscript{122} and other nuclear bodies\textsuperscript{109} that alter the expression of many genes at once (Fig. 3A, B); or 2) expose previously hidden genomic regions to different nucleoskeleton and chromatin associated proteins. Naturally, these options need not be mutually exclusive. Notably, even if the repositioning is only transient, the chromatin and/or transcriptional changes may be sustained long after migration, as a result of enduring post-translational modifications and the prevalence of feedback loops in eukaryotic gene regulation\textsuperscript{115,123-126} (Fig. 3C).

**Future experiments**

We currently lack a systems understanding of the immune system. This is partly because we have not been fully able to mechanistically link the changes that occur as immune cells move between chemically and mechanically defined compartments in the body with the signals they are encountering and their tissue specific roles (Fig. 2). Future experiments need to capture the dynamic nature of the nuclear changes that occur in immune cells when faced with these diverse environments, if we are to understand how mechanical and chemical signals interact during the human immune response.

That chromatin organization provides the link between nuclear shape and gene expression changes is not a new hypothesis,\textsuperscript{51,52,106,127} but it can be approached in a novel way. Analyzing the movement of heterochromatic foci and tagged loci has revealed directional and reproducible movement of chromatin in response to mechanical forces and constraints.\textsuperscript{51,52,74,75,104,110} This movement has even been directly linked to transcriptional changes in a bacterial artificial chromosome introduced into a mammalian nucleus.\textsuperscript{110} However, correlating specific chromatin reorganisation events with gene expression changes in endogenous chromatin may require higher resolution techniques, such as genome-wide chromosome conformation capture (e.g. Hi-C,\textsuperscript{128} GCC\textsuperscript{129}). Unfortunately, Hi-C is destructive and does not allow repeated sampling from the same set of cells. The dynamic nature of the genome\textsuperscript{130} means that single time point sampling will not distinguish between transient changes, stable changes, and stochastic movement of the immune cell genome in response to migration. Microscopic imaging techniques analogous to the brainbow\textsuperscript{131} that allow simultaneous and distinct fluorescent tagging of many genomic loci or transcriptional proteins could allow us to investigate nuclear remodelling during migration.\textsuperscript{104} Other methods of interrogating nuclear organization that allow for repeated and rapid sampling of individual cells would be invaluable.

Immune cell development plays a critical role in human health and disease. Immune disorders have a
clear and quantifiable genetic component. Investigating the spatial organization of DNA in immune cells is a promising method of finding the mechanisms by which autoimmune disease associated SNPs affect the immune system. Mechanical forces affect immune cells at all stages of development, so understanding how these forces act in isolation, and in combination with chemical signals, is critical for understanding how immune cells behave and differentiate in vivo.

Conclusion

Developing a systems understanding of the immune system that enables rapid and reliable therapeutic intervention requires an interdisciplinary approach to immune development that incorporates both mechano- and genome biology.

Abbreviations

- **ECM**: Extracellular matrix
- **Eqtl**: Expression quantitative trait locus
- **GWAS**: Genome wide association study
- **HSC**: Haematopoietic stem cell
- **IFN**: Interferon
- **IL**: Interleukin
- **LINC**: Linker of nucleoskeleton and cytoskeleton
- **MSC**: Mesenchymal stem cell
- **PTM**: Post-translational modification

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Figure 3. Chromatin architecture may translate mechanical forces to gene expression changes. Changes in nuclear shape may affect nuclear activity in several ways. The most simple model (A) shows repositioning of DNA relative to a transcription factory; these changes are rapidly reversible and may not be maintained in the absence of the force in either the structure or the function of the nucleus. (B) Some chromatin remodelling proteins are known to ‘slide’ along DNA. Therefore, pulling on chromatin loops brings 2 or more proteins into close proximity, forming the complexes necessary to initiate transcription. This may result in a stable change to both genome organization and function. (C) Changes in nuclear shape may bring a modifier and its target into contact, allowing a transient change to chromatin architecture to result in a stable change to nuclear function. For simplicity, SUMOylation has been illustrated as the post-translational modification (PTM) of the transcription factor, shown here tethered to the nuclear lamina. Transcription factors and other accessory proteins have SUMO (Small Ubiquitin-like Modifier), ubiquitin, or other PTMs delivered by modifiers which are often tethered to chromatin or nucleoskeleton components. These modifications may activate or repress transcriptional activity, or target the protein for degradation.
SNP  Single nucleotide polymorphism
SUMO  Small ubiquitin-like modifier
TEM  Trans endothelial migration
TGF  Transforming growth factor
Th  T helper (cell)
Th2 LCR  T helper 2 locus control region

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