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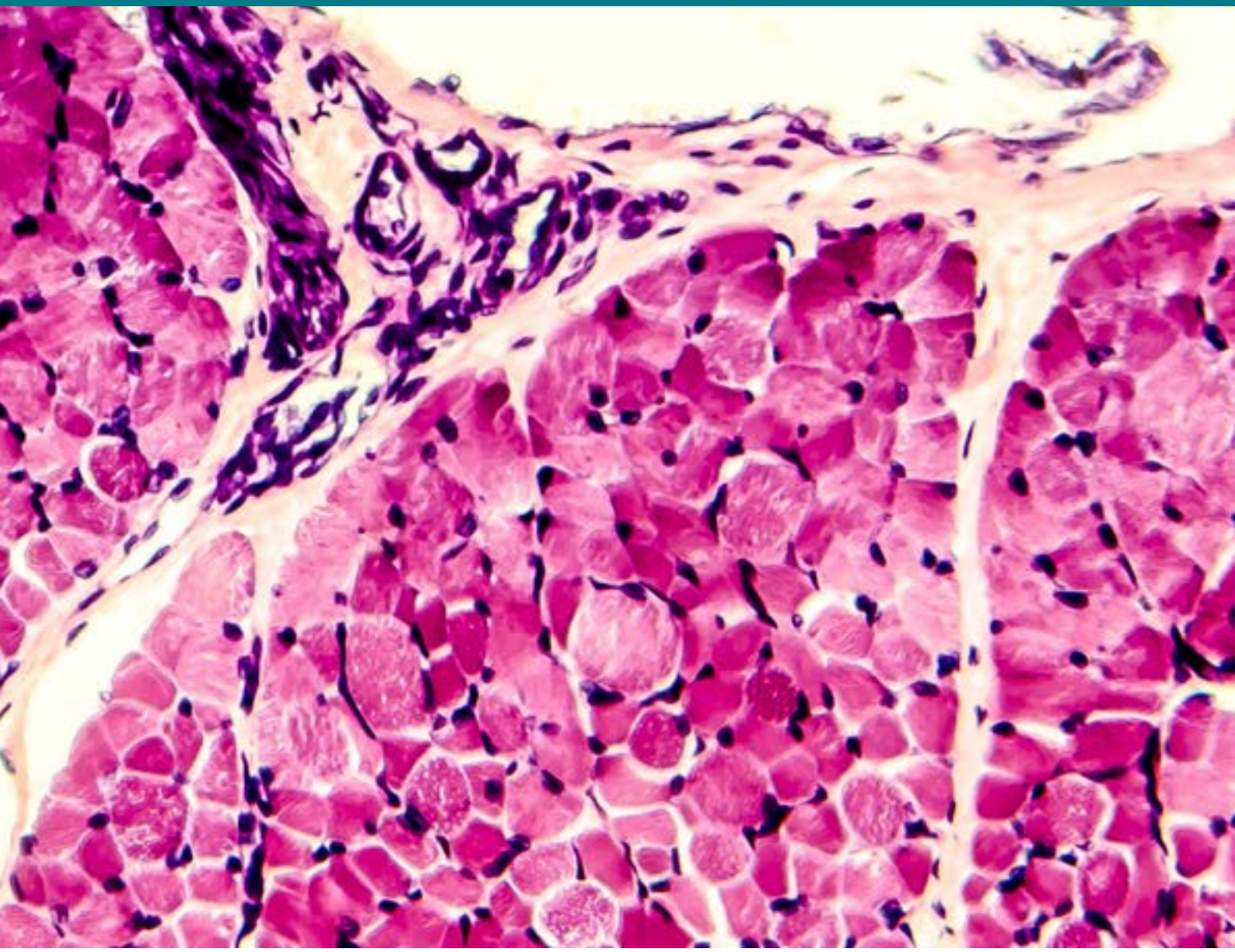

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THE OXIDATIVE ACTIVATION OF Ca^{2+}/CALMODULIN-DEPENDENT PROTEIN KINASE II: A DOUBLE-EDGED SWORD FOR HEALTH AND DISEASE

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ABSTRACT

The Calcium/Calmodulin-dependent protein kinase II (CaMKII) is a versatile signaling protein involved in many cellular processes. It is considered a promising therapeutic target for cardiovascular disease. CaMKII is uniquely capable of integrating various upstream signaling inputs, including redox signals, to regulate a wide range of downstream targets. The activation of CaMKII through the oxidation of a pair of oxidant-sensitive residues in its autoinhibitory region has been established as a significant driver of diseases. However, recent findings suggest that this oxidative activation mechanism is highly conserved and plays critical physiological roles. CaMKII oxidation, thus, is an example of evolutionary trade-offs that confer fitness benefits but also increase disease susceptibility. Understanding how CaMKII oxidation is regulated, and what downstream targets are regulated by oxidized CaMKII will help enhance the benefits while minimizing the detriments of this double-edged sword.

Keywords: CaMKII, redox signal, evolutionary trade-off

RESUMEN

La proteína quinasa dependiente de Ca y calmodulina II (CaMKII) es una proteína de señalización versátil involucrada en muchos procesos celulares y es considera un prometedor blanco terapéutico para la enfermedad cardiaca. La CaMKII es única en cuanto es capaz de integrar diversas vías de señalización rio arriba, incluidas señales redox, para regular diversos blancos rio abajo. La activación de CaMKII a través de la oxidación de un par de residuos sensibles a la oxidación en su región auto inhibitoria, constituye un factor importante en el desencadenamiento de enfermedades. Sin embargo, estudios recientes sugieren que el mecanismo de activación por oxidación es un mecanismo altamente conservado que juega roles fisiológicos críticos. La oxidación de la CaMKII es, es en realidad un ejemplo de compensaciones evolutivas que son beneficiosos pero que también aumenta la susceptibilidad a la enfermedad. La comprensión de cómo se regula la oxidación de la CaMKII y de cuáles blancos corriente abajo son regulados por la oxidación de la CaMKII, ayudara a aumentar los efectos beneficiosos de esta kinasa al mismo tiempo que a minimizar sus efectos adversos.

Palabras clave: CaMKII, señales redox, compensación evolutiva

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Introduction

CaMKII is a multifunctional protein kinase with an impressive list of roles. Some of its roles include regulating cell cycle, death, volume, pH, ion transport, mitochondrial fission, autophagy, lipid and glucose metabolism, learning and memory, cardiac function and skeletal muscle function, fertilization, circadian rhythm, inflammation, and aging (please refer to these excellent recent reviews [1,2]). The diverse role of CaMKII is realized, at minimum, by the combination of two important features. First, CaMKII can phosphorylate various substrates involved in different cellular processes. Second, it can respond to different types of upstream signals, including Ca2+, redox, metabolic signals, and protein-protein interactions. By integrating different signal inputs and regulating diverse downstream substrates, CaMKII acts as a node in the cellular signaling network and impinges on many physiological and pathological processes. In this minireview, I will summarize how CaMKII senses redox signals through a concise molecular mechanism, the implications of this mechanism for health and disease, and the questions that remain to be addressed.

Mechanism of CaMKII oxidative activation

CaMKII sensing a diverse range of upstream signals is a remarkable example of how evolution can create complexity by elaborating a simple mechanism. Fundamentally, CaMKII activity is regulated by the interaction between its kinase domain and the autoinhibitory region of its regulatory domain (Fig. 1). The autoinhibitory region blocks the kinase domain from accessing substrates, thus keeping CaMKII inactive. To activate CaMKII, the autoinhibitory region must be detached from the kinase domain. Evolution has exploited this simple requirement to enable different inputs for CaMKII regulation. As its name suggests, CaMKII is activated by calcium-bound calmodulin (Ca2+/CaM). This is achieved by the presence of a Ca2+/CaM-binding region at the C-terminus of the regulatory domain. When the intracellular Ca2+ concentration rises, Ca2+/CaM binds CaMKII, causing a drastic conformational change of the entire regulatory domain [3] release the autoinhibitory region from the kinase domain, thus activating CaMKII. When Ca2+ concentration drops, CaM dissociates from CaMKII, and the autoinhibitory region rebinds the kinase domain to deactivate CaMKII. Several mechanisms have been discovered that prevent the reassociation between the autoinhibitory region and the kinase domain to maintain CaMKII in an active state, independent of Ca2+/CaM, so-called autonomous activity. Most of these mechanisms rely on post-translational modifications of the autoinhibitory region, which reduces its ability to inhibit the kinase domain. These post-translational modifications include the autophosphorylation of threonine 287 (T287 in CaMKIIβ/γ/δ, or T286 in CaMKIIα), O-GlcNAcylation serine 280 (S280 in CaMKIIδ) [4], nitrosylation of cysteines 280 and 289 (C280 and C289, in CaMKIIα) [5] or C290 (in CaMKIIδ) [6], disulfide bond formation between C273 and C290 (in CaMKIIδ) [7], and oxidation of a pair of methionines (M281/M282, in CaMKIIβ/γ/δ) [8]. Interestingly, these post-translational modifications occur only after CaMKII is initially activated by Ca^{2+}/CaM. Mechanistically, this is probably because these residues need to be exposed for modification. This feature allows CaMKII to integrate Ca^{2+} and other types of signals. In this minireview, I will focus on the oxidation of M281/M282, as these residues are the best studied for oxidative activation of CaMKII, yet many questions still remain to be answered.

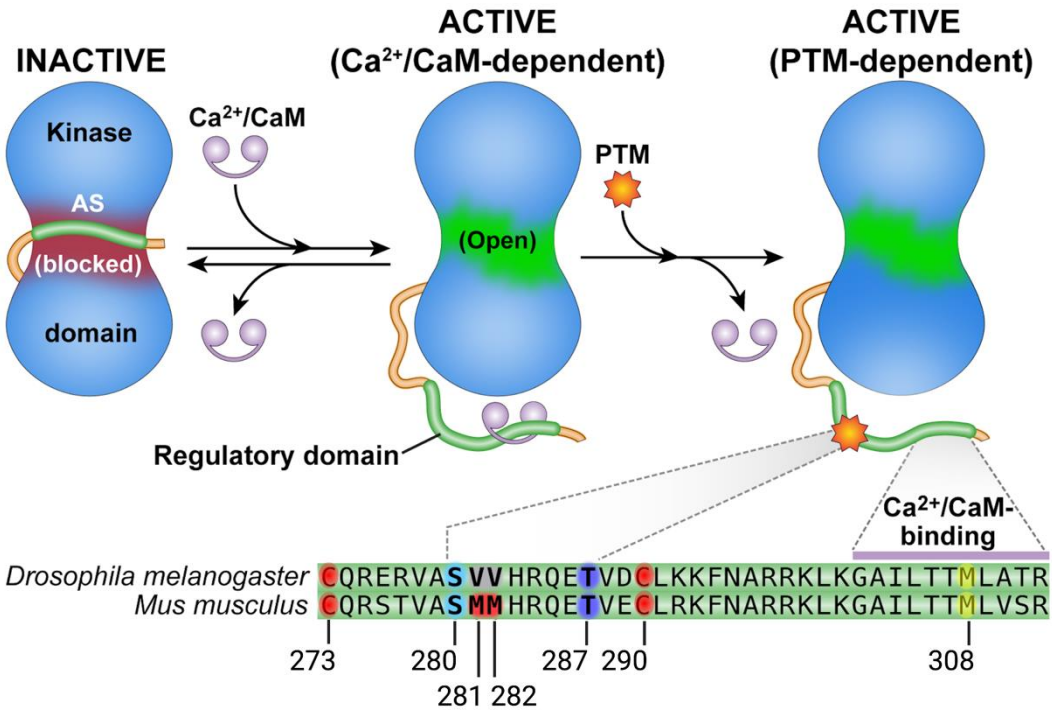

Figure 1. Schematic of CaMKII activation. The kinase domain has an active site (AS) that is occluded by the autoinhibitory region of the regulatory domain. Binding of Ca^{2+}/CaM to the regulatory domain relieves the autoinhibition and activates CaMKII. Post-translational modifications (PTMs) of the autoinhibitory region can maintain CaMKII in an active state even after Ca^{2+}/CaM dissociation. The residues that mediate oxidative activation are highlighted in red. M308 can also be oxidized, which prevents Ca^{2+}/CaM binding and reduces CaMKII activity. This figure is adapted from Fig.1 of Wang et al [23]

Pathological roles of CaMKII oxidation

Early studies indicated that CaMKII was activated under pro-oxidant cellular environment in T cells and cardiomyocytes [9,10], implying that CaMKII was regulated by redox signals. In 2008, Erickson et al. discovered that the oxidation of the M281/M282 (in CaMKIIβ/γ/δ) kept CaMKII in Ca^{2+}/CaM-independent autonomous status [8]. This study also showed that oxidation of the C280/M281 in CaMKIIα, which corresponds to the M281/M282 in other CaMKII isoforms, was also activating. Focusing on the CaMKIIδ, Erickson et al. showed that oxidizing MM residues increased cardiomyocyte death in *vitro* and exacerbated injuries from myocardial infarction *in vivo*. Methionine oxidation adds an oxygen atom to its sulfur atom, forming two diastereomers, methionine-S-sulfoxide and methionine-R-sulfoxide. These diastereomers can be reduced by methionine sulfoxide reductases A (MsrA) and MsrB, respectively [11]. The Erickson study provided evidence that the CaMKII MM oxidation is regulated by MsrA, because deleting MsrA exacerbated the detrimental consequences of CaMKII oxidation. The role of MsrA in limiting CaMKII oxidation was further supported by the observation that MsrA overexpression in the heart protected CaMKII oxidation-induced cardiac rupture [12]. However, whether the MM residues of CaMKII are primarily oxidized to form methionine-S-sulfoxide, or whether MsrA directly reduces oxidized CaMKII is still unknown.

Since this landmark study established CaMKII oxidation as a powerful driver of pathological outcomes, subsequent studies identified a growing list of pathological conditions where CaMKII oxidation plays a detrimental role, such as atrial fibrillation, ischemia/reperfusion injury, cardiac rupture, sinoatrial node (cardiac pacemaker) dysfunction, ventricular arrhythmia, cardiomyocyte death, asthma, and cancer [12–21]. A common theme of these findings is that elevated oxidative stress leads to excessive CaMKII activity to promote detrimental outcomes. However, it is possible that the detrimental effects of oxidized CaMKII are not only dependent on excessive CaMKII activity but also on a unique set of oxidized CaMKII-specific substrates. If this is the case, targeting these substrates may allow the detrimental consequence of oxidized CaMKII to be specifically blocked,

while the physiological functions of CaMKII are maintained. However, before we fully understand these nuances, inhibiting CaMKII kinase activity or preventing CaMKII oxidation may be the simplest intervention in countering the harmful effects of oxidized CaMKII. Because the MM residues are a concise and necessary mechanism for the oxidative activation of CaMKII, they provide an opportunity for gene therapy. Recently, Eric Olson's group used CRISPR-Cas9 adenine base editing to convert the MM residues into a pair of oxidation-resistant valines (VV) in mice, at the time of cardiac ischemia/reperfusion (I/R) and showed that this intervention conferred significant protection against adverse outcomes [22]. This study supports that the MM residues have a critical role in cardiac I/R, similar to our previous observation [16], and also promises an effective intervention to reduce the devastating consequences of I/R injuries and other diseases involving CaMKII oxidation. However, besides its high cost and potential off-target effects, the benefit of permanently disabling the oxidative activation of the "normal" CaMKII needs to be balanced with the risk of impairing the physiological functions of CaMKII oxidation.

Physiological functions of CaMKII oxidation

CaMKII oxidation has been linked to various harmful effects in different diseases. However, we observed that the CM/MM residues that enable CaMKII oxidation are highly conserved in vertebrates, but not in invertebrates [23]. This suggests that CaMKII oxidation emerged in the ancestral vertebrates and conferred evolutionary advantages. We hypothesized that CaMKII oxidation might enhance the motor performance of ancestral vertebrates, which had a more active lifestyle than contemporary invertebrates. To test this hypothesis, we created a knock-in mouse model with oxidation-resistant valines replacing the MM residues in CaMKIIγ, the primary skeletal muscle isoform of CaMKII (VV mice). We found that the VV mice had impaired running performance and Ca2+ handling in their skeletal muscle fibers compared to the wildtype mice. We also demonstrated that skeletal muscle CaMKII is activated by muscle contraction in a manner that depends on oxidants and CaMKII oxidation. Therefore, our study reveals a positive physiological role of CaMKII oxidation in supporting vertebrate motor function and fitness. Remarkably, when we introduced the MM residues to the CaMKII of Drosophila melanogaster (fruit flies), the flies also gained enhanced motor function. This observation suggests that the common ancestors of invertebrates and vertebrates were poised to benefit from CaMKII oxidation to boost motor performance. The absence of CaMKII oxidation in invertebrates thus indicates that its detriments may outweigh its benefits. Consistent with this idea, we observed that the flies with oxidizable CaMKII were more vulnerable to pathological oxidative stress and had a reduced lifespan. These "humanized" flies, recapitulating both the beneficial and detrimental roles of CaMKII oxidation, are a valuable model to investigate the functions of this phenomenon. Since flies only have one CaMKII gene, they can greatly simplify the complexity caused by four CaMKII genes in vertebrates. These flies are also suitable for studying chronic conditions such as aging and will enable genetic screening for regulators and targets of oxidized CaMKII.

Currently, the list of the physiological functions of CaMKII oxidation is still short. Besides regulating exercise performance, we found that CaMKII oxidation regulates the transcriptional responses of skeletal muscles to an acute bout of exercise, and of mast cells to degranulation [23]. Therefore, CaMKII oxidation connects redox signals to gene expression. In cardiomyocytes, CaMKII oxidation may underlie the Anrep effect, where cardiomyocytes enhance contractility in a few seconds when faced with increased afterload [24]. However, more evidence using cardiomyocytes expressing only the oxidation resistant VV versions of CaMKII is needed to support this concept. CaMKII oxidation was also found to play a role in embryonic development, revealed on the RGS6-knockout background [25]. Since CaMKII isoforms play diverse physiological functions, and all vertebrate CaMKII have the CM/MM residues for oxidative activation, I expect that there are many important physiological functions of CaMKII oxidation waiting to be discovered.

The fact that CaMKII oxidation plays physiological roles important for the evolutionary fitness of animals, while also predisposing them to various diseases, many of which are aging-related, supports that CaMKII oxidation is an exemplary case of antagonistic pleiotropy [23]. Antagonistic pleiotropy

is an evolutionary theory of aging proposing that natural selection can select genes that play beneficial roles in younger animals, despite their harmful roles in older animals, and such genes underlie aging [26]. The "humanized" MM flies will be an excellent model to establish the mechanisms by which CaMKII oxidation promotes aging.

Future directions

Despite the extensive research on the oxidation of CM/MM residues, many questions remain. Most importantly, it is still unclear how these residues are oxidized in vivo. Although methionine residues are susceptible to oxidation, the reactivity between methionine and physiologically relevant reactive oxygen species is low [7], which is not compatible with the dynamic roles of CaMKII oxidation in cellular signaling. More likely, CaMKII is oxidized through enzyme-mediated mechanisms. The NADPH oxidases (NOX) are promising candidates for this role because CaMKII oxidation is reduced in NOX-deficient cells [8,23]. Potentially, a fraction of CaMKII is near NOX and thus is exposed to a high local concentration of reactive oxygen species that promote rapid oxidation. The other potential regulators of CaMKII oxidation are the MICAL family of protein methionine oxidases. A member of this family of proteins, MICAL1, which had been shown to regulate actin polymerization by oxidizing methionine residues in actin [27,28], was examined by the Mark Anderson lab for its ability to activate CaMKII by oxidizing the MM residues [29]. Unexpectedly, MICAL1 was found to oxidize M308, which is localized in the Ca2+/CaM binding region of CaMKII. This oxidation, instead of activating CaMKII, significantly reduced the Ca2+/CaM-dependent activation of CaMKII [29]. This breakthrough study suggests that oxidative reaction could restrain the excessive CaMKII activity under pro-oxidant conditions, but still leaves the identity of enzymes oxidizing the MM residues unknown. Future studies may further examine the role of the other MICAL family members and other enzymes of similar catalytic mechanisms.

The effort to identify enzymes oxidizing CaMKII will benefit from better tools that detect oxidized CaMKII. In their initial study, Erickson et al. developed a polyclonal antiserum that reacted with oxidized CaMKII [8]. However, a recent study showed that this antiserum does not directly recognize oxidized MM residues; instead, it recognizes a disulfide bond between C273 and C290 formed during oxidant treatment [7]. It is possible that the formation of the C273-C290 disulfide bond is highly correlated with MM oxidation in vivo, but developing specific reagents for oxidized MM residues will be necessary for the field to progress further. The fluorescence resonance energy transfer (FRET) based sensor, Camui [30,31], has been used to study the post-translational regulation of CaMKII activation [32,33], but this sensor reports CaMKII conformational changes rather than activity. Alternatively, the Anderson lab develop two fluorescent protein-based sensors that report CaMKII activity [23,34], but these sensors cannot differentiate CaMKII activity elicited by different modes of upstream inputs. The Gladyshev lab developed fluorescent sensors that report protein methionine oxidation [35], but these sensors lack specificity to CaMKII oxidation. Future reporters that combine the advantages of these sensors will be especially useful.

It has been fifteen years since the initial discovery that oxidizing the CM/MM residues activate CaMKII [8]. Initially considered a detrimental feature, CaMKII oxidation is now recognized as a vertebrate-specific and highly conserved mechanism that bridges redox signals to physiological outcomes. Future studies will likely identify many other physiological and pathological processes involving CaMKII oxidation. Understanding how this process is regulated, and what substrates are regulated by oxidized CaMKII will bring new opportunities to retain the benefits of CaMKII oxidation while minimizing its detriments.

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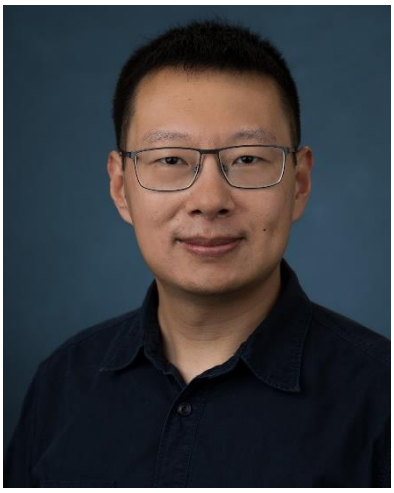

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