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The Myc and Ras Partnership in Cancer: Indistinguishable Alliance or Contextual Relationship?

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Abstract

Myc and Ras are two of the most commonly activated oncogenes in tumorigenesis. Together and independently they regulate many cancer hallmarks including proliferation, apoptosis and self-renewal. Recently, they were shown to cooperate to regulate host tumor microenvironment programs including host immune responses. But, is their partnership always cooperative or do they have distinguishable functions? Here, we provide one perspective that Myc and Ras cooperation depends on the genetic evolution of a particular cancer. This in turn, dictates when they cooperate via overlapping and identifiably distinct cellular and host immune dependent mechanisms that are cancer type specific.

Introduction

Myc and Ras are biologically distinguishable and yet interdependent and cooperate both physiologically in normal cells and tissues and pathologically during tumorigenesis. Myc is a family of transcription factors—c-, l-, and n-Myc, whereas Ras is a family of GTPases—H-, K-, and N–Ras. Myc generally localizes to the nucleus while Ras localizes to the cytoplasm. Myc primarily regulates gene transcription, albeit has a cytoplasmic function, while Ras regulates protein signaling through phosphorylation cascades. However, both cooperate to control other biological pathways that influence diverse cellular and host programs from proliferation and apoptosis to metabolic programming, cellular senescence, self-renewal, genomic integrity, angiogenesis, immune surveillance and adaptive and innate immunity. Hence, in normal cells, Myc and Ras clearly required careful regulation because they have diverse and rather omnipotent functional effects on individual cells that drive host phenotypes.

Myc and Ras activation frequently contributes to tumorigenesis. They are driver oncogenes that can initiate tumorigenesis. The combined activation of Myc and Ras have been shown to cooperate to cause tumorigenesis experimentally, as pioneered by Land, Weinberg, and

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colleagues in 1986. Yet, since this time, the manner in which Myc and Ras cooperate has become increasingly complex. Here we provide one possible perspective that what dictates how Myc and Ras cooperate depends upon the genetic evolution and context of a particular tumor. We discuss a few recent published examples, each from a different cancer type, that are illustrative of the range of observed mechanistic interactions.

Myc and Ras Cooperative Relationship

A multitude of mechanisms have been proposed over the last two decades on the relationship between Myc and Ras in tumorigenesis, corresponding with the emergence of new scientific areas of understanding. Thus, the emergence of the importance of apoptosis in cancer biology, led to the insight that oncogenic Ras suppresses apoptosis induced by Myc via activation of the PI3K/AKT pathway. Yet, Ras itself can induce pro-apoptotic pathways in the same cells via Raf pathway activation[1]. This dual function of Ras points to the tight regulation of Ras and Myc in normal cells and emphasizes their shifting effects depending on the context and the net effect of intracellular pathways.

Ras as well as other members of the signaling cascade have been shown to regulate Myc protein stability through the regulation of specific phosphorylation residues[2]. As such, Ras induces the phosphorylation of Myc at serine 62 (Ser62) stabilizing Myc and promoting its transcriptional activities. To stop transcription, Myc is then phosphorylated at threonine 58 (Thr58) to release Myc from DNA. Upon Ser62 phosphorylation removal, Thr58-phosphorylated Myc is ubiquitinated and subsequently degraded[2]. During malignant transformation, mutated Ras enhances Myc Ser62 phosphorylation preventing Myc protein degradation and increasing Myc protein stability.

Since then, multiple reports have suggested that Myc and Ras cooperate through more nuanced effects on what happens inside cancer cells and through regulation of the host tumor microenvironment and immune system. Thus, Myc and Ras work together through several cancer hallmarks, but also through effects on host immune responses to cancer via regulation of immune checkpoints, cellular cytokines, and cellular mediated immunity, as described in more detail below.

Here, we review and discuss recent mechanisms by which Myc and Ras have been shown to cooperate to cause cancer. We then analyze how the nature of the cooperation between Myc and Ras depends on specific genetic evolution and context in particular cancers. We also discuss whether this cooperation occurs via similar overlapping and/or identifiably distinct intracellular and host immune dependent mechanisms that may explain when the growth of a particular cancer is dependent upon Myc and/or Ras.

To discuss these concepts and pinpoint the molecular nodal points that account for the partnership of Myc and Ras to maintain a cancer phenotype, we will discuss three cancer types to provide a variety of scenarios to illustrate the different functional aspects of Myc and Ras and their cooperative relationship in driving cancer development and cancer progression.

Myc and Ras Cooperation in Hematopoietic Tumorigenesis

Myc and Ras cooperate to cause hematological malignancies as first experimentally shown by Cory and Adams over 20 years ago. Importantly, Myc overexpression is much more capable than mutated Ras at initiating lymphomagenesis, but both together cooperate to accelerate tumorigenesis. Hence, Myc and Ras in hematologic malignancies appear to cooperate but likely work through non-overlapping mechanisms to cause these tumors. Myc or Ras driven tumors both regress upon Myc or Ras inactivation, respectively; and, tumors overexpressing both Myc and Ras regress either when both oncogenes are inactivated or when only Myc is suppressed (Felsher laboratory, *unpublished findings*). Hence, in hematologic malignancies such as lymphoma, Myc appears to drive tumorigenesis in a manner that can cooperate with Ras, but Ras must be contributing in a non-overlapping mechanism that does not functionally overlap with Myc. One possible explanation for these findings is that Ras in this tumor context is largely functioning by cooperating with Myc to suppress immune surveillance[3] by $CD4^+$ T cells and natural killer (NK) cells[4] but that this function is no longer essential once a tumor has arisen and can outpace an immune response.

Myc and Ras Cooperation in Breast Cancer

Myc and Ras expression in mammary epithelial cells cooperate to elicit breast adenocarcinoma where the frequency of mammary epithelial cell transformation and neoplastic foci formation is increased. Notably, in contrast to hematological tumors, Myc inactivation in breast cancers results in tumor regression but dormant tumor cells persist, as reported by Boxer, Chodosh, and colleagues[5]. Over 60% of mammary adenocarcinomas that were able to grow independent of Myc acquired Ras mutations resulting in Ras overactivation. In breast adenocarcinoma, Ras mutations appears to be able to functionally replace Myc overexpression to maintain tumorigenesis. In this context, Myc and Ras may function through overlapping mechanisms to maintain tumorigenesis and promote tumor growth. These mechanisms may include changes in tumor cell intrinsic pathways (e.g. increased cellular proliferation and/or apoptosis inhibition) as well as changes in host immune responses, as has been described in hematopoietic tumors[4]. The nature of immune mechanisms that are negatively affected by Myc and/or Ras expression in mammary adenocarcinomas remains understudied.

Myc and Ras Cooperation in Lung Adenocarcinoma

Several recent reports have interrogated how Myc and Ras cooperate to both initiate and maintain lung adenocarcinoma[6,7]. Most recently, Myc and $KRas^{G12D}$ have been shown together to cooperate to cause lung adenocarcinoma through a multitude of effects on the immune response including regulation of immune checkpoints such as programmed death-ligand 1 (PD-L1)[6], but also through effects on immune cell recruitment (B cells, T cells, and NK cells), major histocompatibility complex I (MHC I) expression[4], and cytokine production (e.g. interferon alpha (IFNα), C-C motif chemokine ligand 2 (CCL2), and interleukin 13 (IL13))[6]. Thus, there are likely many mechanisms by which Myc and Ras co-regulate the immune response.

However, Myc and Ras appear to have different roles in maintaining lung tumor growth[6,7]. In tumors caused by $KRas^{G12D}$, the inactivation of this oncogene results in rapid tumor regression[6,7]. In contrast, in lung cancers caused by Myc alone, the inactivation of Myc has a relatively modest ability to induce tumor regression[7]. Similarly, Myc inactivation alone in $KRas^{G12D}$ and Myc overexpressing lung cancer results in rapid tumor regression back to the size of tumors expressing $KRas^{G12D}$ that then remained quiescent indefinitely[6]. In contrast, in lung tumors initiated by both Myc and Ras, inactivation of both oncogenes results in dramatic tumor regression[6,7]. Thus, how Myc and Ras initiate and maintain lung cancer depends upon the evolutionary and genetic context where they arise.

How can one reconcile, when and why are both Myc and Ras required to maintain lung tumorigenesis? One explanation is that whether both Ras and Myc are required to maintain lung adenocarcinoma depends upon the continued activation of the downstream signaling cascade of the Janus tyrosine kinase/Signal transducer and activator of transcription (JAK/STAT) pathway which has been shown to be regulated by both Myc and Ras. Thus, Ras activation appears to be critical to elicit STAT3/5 activation. In tumors caused by Ras alone or by both Myc and Ras, the inactivation of Ras alone or the inactivation of both Myc and Ras, respectively can inactivate STATs and accelerate tumor regression. In tumors caused by Myc alone, inactivation of Myc does not inactivate the STAT pathway[7].

Presumably, then if a lung adenocarcinoma acquires the ability to activate STAT signaling either through Ras genetic mutations or through activation of other gene products in the signaling cascade has vital mechanistic consequences for the dependence of that tumor on Ras and/or Myc for sustained tumorigenesis. Finally, the recent appreciation that Ras and Myc also regulate the immune response, suggests that another possible and non-mutually exclusive mechanism is that these same signaling pathways, such as, STAT activation or immune checkpoint regulation, also influence the ability of lung tumors to evade the immune responses.

A Contextual Interaction

Myc and Ras appear to cooperate to initiate and maintain cancer through different mechanisms in particular cancers. The different observations in hematological, breast, and lung cancer reflect functional differences related to tissue specific tissue context, differences in the evolutionary genetic trajectory of these cancers, and the tumor microenvironment and immune status of a particular tumor.

How Myc and Ras cooperate to initiate and maintain cancer may generally depend upon whether Myc, Ras, or different oncogenes are the primary cancer driver. Cancers driven by Myc or Ras alone or both Myc and Ras show a differential dependence for sustained tumor growth. These differences may reflect on whether the JAK/STAT signaling pathway becomes activated through genetic events, or epistatically through Ras and/or MYC.

Whether Ras itself or other oncogenes in signaling pathways are required to maintain increased Myc protein stability and activity may also play a key role in how Myc and Ras cooperate to maintain a cancer. These mechanisms would influence the way in which Myc

and Ras affect intracellular signaling in tumor cells and host immune surveillance. The genetic evolution of a cancer is likely to define in what manner Myc and Ras cooperate and synergize and whether or not they are mutually required to maintain a cancer.

Further Considerations of the Myc and Ras Cooperation

How Myc and Ras cooperate to initiate and maintain tumorigenesis likely depends upon mechanisms more than JAK/STAT signaling, coordinated regulation of Myc protein stability, and cooperative effects on immune surveillance. Other possible mechanisms include the specific genetic context of particular tumors that would dictate whether sustained activity of Ras or Myc is required to maintain a cancer phenotype. The specific alleles and genetic mutations of the Myc and/or Ras genes are also likely to influence how and when sustained activity of these oncogenes is required.

Myc and Ras have multiple alleles that may contribute to how these oncogenes initiate and maintain cancer. For Myc, there are c-, n- and l- alleles that have been associated with specific cancer types and are likely functionally different. For Ras, the H-, K-, and N- alleles have been associated with particular cancer types and they may not be functionally identical. Also, specific genetic mutations may be associated with the activation of different oncogenic pathways. For example, mutations in Ras in codons 12, 13, or 61 seem to regulate different intracellular pathways including the PI3K/Akt vs Raf/ERK pathways[8]. Likewise, H-Ras compared with K-Ras has been shown to be better at activating the PI3K pathway while the latter is a better Raf pathway activator[8]. Additionally, different Ras isoforms respond differently to signaling factors. As such, mutant N-Ras, rendered colon cancer cells resistant to apoptosis in response to tumor necrosis factor alpha (TNFα) while mutant K-Ras did not respond to TNFα in the same manner[8]. Thus, for Ras, and likely for Myc, specific alleles and mutations are expected to influence how these oncogenes initiate and maintain cancer.

Some additional open questions include: Does the order in which Ras and Myc become genetically activated in a cancer dictate the relationship and interaction between the two oncogenes? This could influence whether Ras is required to epistatically activate Myc through increased protein stability[2]. Does suppression of Myc and Ras back to physiological levels suffice to induce tumor regression or is complete suppression required to elicit sustained regression? In tumors, in which Myc and/or Ras are drivers even partial suppression of oncogene expression has been shown to elicit tumor regression[6,7]. Whether this is dependent upon the genetic activation of Myc or Ras or the initiating driver oncogene is unclear. When there is brief suppression of Myc or Ras to reverse a cancer, can resumption of oncogenic activity restore tumorigenesis? Some literature suggests that even brief and partial Myc suppression result in sustained tumor regression and other reports suggest that tumors can recur upon restoration of Myc expression[3,7,9]. Finally, what are the precise gene activation levels that are required for Myc and Ras? And, are these levels different for tumor initiation and maintenance? Further investigation in these areas is necessary.

Finally, although it has been extensively shown that Myc and Ras coordinate to influence proliferation, apoptosis, senescence, stemness, and more recently immune surveillance

regulation in cancer; in understanding how Myc and Ras cooperate, other cellular programs may be considered as they may be equally important including cellular metabolism[9] and exosome assembly and function[10]. One could speculate that Myc and Ras may more broadly influence the tumor microenvironment, and this could include interactions between tumors and host microbiome, amongst other possible mechanisms.

Therapeutic Implications

Myc and Ras are mutated and/or overexpressed in the majority of human cancers making them desirable therapeutic targets. Experimentally inhibiting Myc and Ras can be sufficient to induce sustained tumor regression[6,7,9], but no drugs that directly target Ras or Myc have made it to the clinic. However, as we describe above, there appears to be definable circumstances when targeting Myc and/or Ras would be synergistic and therapeutically effective.

Therapeutically targeting Myc and/or Ras in a particular malignancy is likely to be cancer type and even tumor specific. Some probabilities include that Myc and Ras associated tumors with particular signaling in JAK/STAT or other signaling molecules may be more sensitive to targeting Ras or both Myc and Ras. Second, Myc and Ras associated cancers with high Ser62-phosphorylated Myc levels may be more susceptible to Ras inhibition than Myc inhibition since the former will exponentially reduce Myc levels by inducing Myc degradation resulting in rapid tumor regression while the latter will result in a linear reduction of Myc and slower tumor regression. Third, Myc and Ras influence expression of immune regulators such as PD-L1 or as more recently suggested MHC I[4] which directly affect their relative sensitivity to immune therapy.

The manner in which Myc and Ras cooperate to initiate and maintain cancer is likely to be causally influenced by genetic events and the evolutionary context in which these oncogenes are activated in a particular cancer. In turn, these events will influence the intracellular pathways and host immune responses taking place in the tumor. The nature of these mechanistic interactions will dictate how and when therapies that target Myc and/or Ras are effective and will further implicate specific immune and biological therapies.

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