Research Interests
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SUMMARY OF PAST RESEARCH

Apoptosis was a mysterious process in the early nineties. A debate raged as to how the TNF receptor TNFR1 and its close homologue Fas engaged the suicide pathway. The first breakthrough was the demonstration from the Dixit laboratory that a cysteine protease (now termed caspase) was a component of the death receptor-induced apoptotic pathway (Tewari, *JBC*, 1995, citations: 664). These observations set the stage for the identification of YAMA, or caspase-3, as the key downstream executioner protease (Tewari, *Cell*, 1995, citations: 2,272), although this then begged the question of how it was engaged by death receptors. Other surface receptors functioned as ion channels or by altering intracellular phosphorylation events but death receptors signaled apoptosis by an entirely new mechanism. Specifically, an adapter protein termed FADD recruited and activated an initiating death protease termed FLICE/caspase-8 (Chinnaiyan, *Cell*, 1995, citations: 2,516 and Muzio, *Cell*, 1996, citations: 3,030). In other words, the second messenger emanating from the death receptor was a protease! These papers, designated citation classics, resulted in Dr. Dixit being the second most highly cited scientist in 1996.

Subsequently, his laboratory promulgated the "induced proximity model" as a mechanism for the activation of caspase zymogens (Muzio, *JBC*, 1998, citations; 1,105), showed that the FADD/caspase-8 pathway was indeed the central apoptotic conduit used by all death receptors (Pan, *Science*, 1997, citations: 1,586), revealed TRAF3 to be a CD40 signaling adaptor (Hu, *JBC*, 1994; citations: 351), demonstrated that MyD88 was a key adaptor in innate immune signaling (Muzio, *Science*, 1997, citations: 1052), discovered Paracaspases and Metacaspases, one of which plays a central role in MALT lymphoma (Uren, *Mol Cell*, 2000, citations: 842), provided the first evidence of ephrin system involvement in angiogenesis (Pandey, Science,1995, citations: 327) and established that NOD proteins possessing a death-fold are critical components of the inflammasome complex (Mariathasan, *Nature*, 2004, citations: 1,077 and Mariathasan, *Nature*, 2016, citations: 1,463). A20, an increasingly important negative regulator of NF-kappaB signaling incontrovertibly linked to human autoimmune disorders, was first discovered and characterized by his laboratory (Opipari, *JBC*, 1990, citations: 331 and Krikos, *JBC*, 1992, citations: 368) and shown to possess ubiquitin editing activity (Wertz, *Nature*, 2004, citations: 1,122) using isopeptide-linkage specific antibodies (Newton, *Cell*, 2008, citations: 327). Most recently, his group has discovered the non-canonical Inflammasome pathway that responds to the presence of intracellular LPS independent of toll-like receptors (Kayagaki, *Nature*, 2011, Kayagaki, *Science*, 2013 and Kayagaki, *Nature*, 2015).

Much of what is described herein is documented in three accounts published in *Nature* (2008, 453:271-273), *Nature Cell Biology* (2010, 12(5): 415) and *The Journal of Immunology* (2013, 190:3-4). These accounts highlight the pervasive excitement in the heydays of apoptosis research and Dr. Dixit's pivotal role.

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